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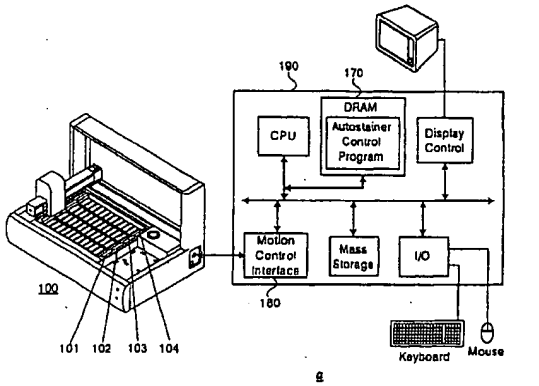

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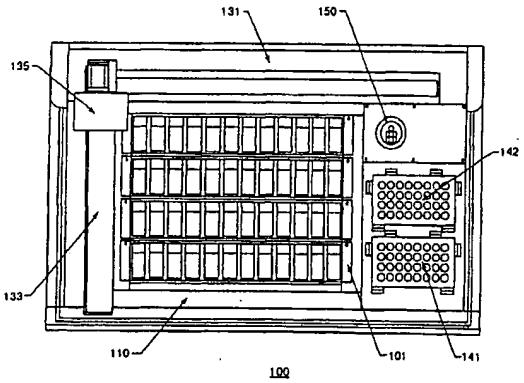

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(57) Abstract: To simplify the process of preparing microscope slides, an advanced automatic staining apparatus (100) is disclosed. The disclosed automatic staining apparatus (100) comprises an electromechanical automatic staining device that is coupled to a personal computer system (190) using an interface card (180). An autostainer control program (170) runs on the personal computer system (190). The autostainer control program (170) allows a user to simply program the automatic staining apparatus (100) using simple commands entered in the graphical user interface. The autostainer control program (170) includes several features that simplify the programming such as safeguards that ensure compatible reagents are being used; automatic buffer solution requirement calculator; and the ability to determine optimal staining procedure. The electromechanical automatic staining device includes features such as dual waste bins for hazardous and nonhazardous waste storage, an automatic dispenser cleansing system; and unique slide clip that minimizes capillary effect.

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METHOD AND APPARATUS FOR AUTOMATIC TISSUE STAINING

Field of the Invention

The present invention relates to the field of medical lab equipment. In particular the present invention discloses a fully automated system for staining tissue specimens and cell preparations.

Background of the Invention

It is often difficult to examine unstained cell and tissue preparations with a microscope due to a lack of contrast between individual cells and the background matrix, or between individual parts of cells. To improve the contrast, researchers have applied stains to cell and tissue specimens to be examined. The stains are absorbed differently by the various structures in cells such that the contrast between the different cell structures is improved.

Staining tissue specimens is a nontrivial time-consuming process. Often a number of different staining and rinsing stages are required. Each stage requires a specific amount of reagent or buffer and takes a specific amount of time. Thus, trained technicians are often employed to perform such operations. Furthermore, hospitals and laboratories must stain large numbers of tissue specimens. Thus, it is desirable to automate the tissue specimen staining process. By automating the process, expensive human labor is eliminated and the probability of an error occurring during the staining process is reduced. Accordingly, a few manufacturers have introduced equipment for the automated staining of tissue specimens on microscope slides.

Existing automatic staining devices are not very simple to use. Arcane programming commands and complicated procedures require extensive user training before such devices can be operated effectively. It would therefore be desirable to simplify the operation of an automatic staining device.

Summary of the Invention

The present invention comprises an automatic staining apparatus coupled to a personal computer system running an operating system with a graphical user interface. The personal computer system includes an interface card that is used to control the automatic staining apparatus. An autostainer control program runs on the personal computer system. The autostainer control program allows a user to simply program the automatic staining apparatus using simple commands entered in the graphical user interface. The autostainer control program also includes a Stat function that allows the user to interrupt the routine staining of slides in order to prioritize processing of one or more slides that require immediate analysis. The invention simplifies the process of programming an automatic staining apparatus to include staining of stat slides.

Other objects, features, and advantages of present invention will be apparent from the accompanying drawings and detailed description.

Brief Description of the Drawings

The objects, features and advantages of the present invention will be apparent to one skilled in the art, in view of the following detailed description in which:

Figure 1a illustrates a perspective view of the autostainer **100** apparatus.

Figure 1b illustrates a top view of the autostainer **100** apparatus.

Figure 2 illustrates a cut-away top view of the internal components of the autostainer **100** apparatus.

Figure 3a illustrates a top view of a slide rack for the autostainer.

Figure 3b illustrates a front view of a slide rack for the autostainer.

Figure 3c illustrates a close-up perspective view of a slide rack for the autostainer.

Figure 4a illustrates a side view of the Z head assembly for the autostainer.

Figure 4b illustrates a front view of the Z head assembly for the autostainer.

Figure 5a illustrates a top view of the air nozzle.

Figure 5b illustrates a left side external view of the air nozzle and the nozzle lip.

Figure 5c illustrates a front view of the air nozzle.

Figure 5d illustrates a right side cutaway view of the air nozzle and the nozzle lip.

Figure 5e illustrates a view of the air nozzle tip.

Figure 5f illustrates a bottom view of the air nozzle.

Figure 5g illustrates a left side external view of the air nozzle with the nozzle lip in place.

Figure 5h illustrates a front view of the air nozzle.

Figure 6 illustrates the Sign-In Screen of the autostainer control program.

Figure 7 illustrates the Options Screen of the autostainer control program.

Figure 8 illustrates the Initialize Screen of the autostainer control program.

Figure 9a illustrates the Program Staining Run Screen of the autostainer control program.

Figure 9b illustrates the Program Staining Run Screen with a Print Report dialogue box displayed.

Figure 10 illustrates the Patient Information Screen of the autostainer control program.

Figure 11 illustrates the Protocol Template Design Screen of the autostainer control program.

Figure 12 illustrates an Edit Individual Slide Reagent Screen of the autostainer control program.

Figure 13 illustrates the Edit Individual Slide Reagent Screen of **Figure 12** with the fields filled in.

Figure 14 illustrates the Program Staining Run Screen of the autostainer control program with an autoprogramming pop-up window displayed.

Figure 15 illustrates the Program Staining Run Screen of the autostainer control program with a Detection Kit list for a selected Detection Kit step.

Figure 16 illustrates the Program Staining Run Screen of the autostainer control program with an incompatible reagent warning dialogue box.

Figure 17 illustrates the Edit Reagent List Screen of the autostainer control program.

Figure 18 illustrates the Program Staining Run Screen with a Save Current Program dialogue box.

Figure 19 illustrates the Slide Layout Map Screen of the autostainer control program.

Figure 20 illustrates the Slide Layout Map Screen of the autostainer control program.

Figure 21 illustrates a summary of the scheduling system of the autostainer control program.

Figures 22a through **22d** list the details of adding a new group to the Currently Scheduled Array.

Figure 23 illustrates the Run Time Calculation Window and the Run Time Dialogue Window of the autostainer control program.

Figure 24 illustrates the Reagent Layout Map Screen of the autostainer control program.

Figure 25 illustrates the Reagent Layout Map Screen of the autostainer control program with a reagent list window displayed.

Figure 26 illustrates the Set Start Time Window of the autostainer control program.

Figure 27 illustrates the Run Log Screen of the autostainer control program.

Figure 28 illustrates a program initiating the Stat function.

Figure 29 illustrates a Timer Message for the Stat function.

Figure 30 illustrates the initial steps in implementing a Stat staining program.

Figure 31 illustrates additional steps in implementing a Stat staining program.

Figures 32a-32g illustrates embodiments for programming Stat slides.

Detailed Description of the Preferred Embodiment

A method and apparatus for automatically staining tissue specimens are disclosed. In the following description, for purposes of explanation, specific nomenclature is set forth to provide a thorough understanding of the present invention. However, it will be apparent to one skilled in the art that these specific details are not required in order to practice the present invention. For example, the present invention has been described with reference to staining of tissue specimens. However, the same techniques can easily be applied to other types of slide preparation work. Also as known to one skilled in the art, staining includes application of reagents to effect immunological as well as biochemical reactions, and thus is defined broadly.

The Autostainer Hardware

Figure 1a illustrates a perspective view of the autostainer **100** apparatus of the present invention. The autostainer **100** is used for staining tissue specimens that are placed onto glass slides. In the embodiment illustrated in **Figure 1a**, there are four slide racks **101**, **102**, **103**, and **104**. Each slide rack is capable of holding twelve slides such that the autostainer **100** of **Figure 1a** can perform operations on forty-eight slides at once.

The autostainer **100** of **Figure 1a** has a robotic delivery system that delivers reagents, buffer solutions, and air to the glass slides. The robotic delivery system is controlled by a motion control interface card **180** in a personal computer system **190**. The personal computer system **190** runs an autostainer control program **170** that sends control commands through the motion control interface **180** to control the robotic delivery system.

Figure 1b illustrates a top view of the autostainer **100**. Referring to **Figure 1b**, the robotic delivery system of the autostainer **100** consists of an X axis mechanism **131**, a Y axis mechanism **133**, and a Z head **135**. The Z head **135** has a buffer tube for dispensing buffer rinse solution, a blow nozzle to blow air onto slides, and a probe for picking up reagents that will be placed onto the glass slides. The various reagents are stored in the reagent racks **141** and **142**.

To prevent contamination, the probe is cleaned in a reagent probe wash bin **150** between the use of different reagents. The wash bin **150** has three different receptacles that are used in three stages. The first hole is used to rinse the inside of the probe by forcing buffer rinse solution through the inside of the probe and down into a first drain receptacle. The second receptacle is used to clean the outside of the probe by forcing buffer rinse solution through the inside of the probe while the probe is in the tightly confined second receptacle such that the buffer solution is forced upward on the outside of the probe. Finally, the probe is placed into a third receptacle and air is forced through the probe to clean out the buffer rinse solution.

Beneath the slide racks of the autostainer **100** is a sink assembly **110**. The sink assembly catches the reagents and buffer rinse solution that drip off the slides. **Figure 2** illustrates a cut-away top view of the internal components of the autostainer **100** apparatus. As illustrated in **Figure 2**, a waste reservoir **210** that sits beneath the sink assembly collects the waste. The waste is pumped out of the waste reservoir **210** using a first waste pump **215** or a second waste pump **217**. Two different waste pumps are used such that one waste pump is used to remove nonhazardous waste and the other waste pump is use to remove hazardous waste.

Several other components are also located inside the autostainer. Referring to **Figure 2** a buffer valve **231** and a buffer pump **233** are used to provide buffer rinse solution to the Z head assembly. An air compressor **240** is used to provide compressed air to the Z head assembly. An electronic controller box **250** stores a set of electronic components including the stepper motor drivers for the X, Y, and Z axes.

Autostainer Slide Racks

The slide racks for the autostainer of the present invention have been designed for optimum performance. **Figure 3a** illustrates a top view of a slide rack that is used in the autostainer. The slide rack **300** has twelve slide positions **310** such that the slide rack **300** can hold twelve slides. The slides may be standard U.S. or international sized slides. The slide rack can be carried using the handles **330** on each end of the slide rack **300**. **Figure 3b** illustrates a front view of the slide rack **300**.

Figure 3c illustrates a close up view of four slide positions on a slide rack. Each position is shaped to accept a standard U.S. or an international sized slide **360**. To hold the slide **360** in place, each slide position includes a stainless steel spring clip **320**. The spring clip **320** is wide enough to accommodate common bar coding designations. The stainless steel spring clip **320** suspends the slide **360** by the frosted region **361** of the slide **360**. Since the slide **360** is held only in the frosted region **361** of the slide, the slide rack **300** does not interfere with the specimen or any of the applied reagents. Specifically, since there is no contact with the specimen area (the nonfrosted area), there is no capillary effect, observed in prior art systems, that draws off the reagent. Each slide position **310** is separated from the next slide position by a divider **350**. The divider **350** prevents reagent or buffer from one slide overflowing onto an adjacent slide. Each slide position **310** includes two drain holes **360** for draining excess buffer rinse solution that may reach the areas where the slide is clipped to the slide rack.

Z Head Assembly

Referring back to **Figure 1b** the autostainer **100** has a Z head assembly **135** that carries the buffer dispensing tube, the blow nozzle, and the reagent probe. **Figures 4a** and **4b** illustrate a close-up of the Z head assembly. There are two different assemblies that move along the Z axis on the Z head: the reagent probe assembly and the air/buffer assembly.

The reagent probe assembly comprises the reagent probe **411**, the reagent leadscrew nut block **417**, and the reagent leadscrew **419**. The reagent probe **411** is Teflon coated. The Teflon coating protects the stainless steel probe from corrosion and prevents reagent from sticking to the inside and outside walls of the probe. The reagent probe **411** includes custom circuitry that allows the reagent probe **411** to sense liquid levels. Since the reagent probe **411** can sense liquid levels, the probe goes into reagent vials only deep enough to obtain the desired amount of reagent. By only going deep enough to obtain the desired

amount of reagent, the amount of contamination of the outside of reagent probe **411** is kept to a minimum. Furthermore, since the reagent probe **411** can sense liquid levels, it can determine if there is enough reagent in a vial to complete a staining run. This will be described in greater detail later.

The air/buffer assembly comprises the buffer tube **421**, the air tube **422**, the air nozzle **423**, the air/buffer leadscrew nut block **427**, and the air/buffer leadscrew **429**. Since the reagent probe assembly and the air/buffer assembly are used independently, both assemblies can be driven by the same stepper motor driver **433**. The entire Z Head assembly is constructed in a modular form such that it can be replaced as a single unit.

Autostainer Air Nozzle

The air nozzle on the Z head **135** of the autostainer has been designed to uniformly distribute air across the surface of a glass slide such that an optimal amount of residual buffer solution remains to keep the specimen hydrated. This allows for accurate and consistent staining. **Figures 5a** through **5h** illustrate the air nozzle. **Figure 5d** illustrates a cut-away side view of the air nozzle. The air nozzle has an air shaft **511**, a well **513**, and a nozzle slit **521**. The nozzle slit forms a narrow opening when the nozzle lip **515** is coupled to the nozzle. The well **513** disperses the air such that uniform air flow is delivered out of the nozzle slit opening. The distribution angle of the nozzle allows the Z head to be narrower than prior art systems. Since the Z head is narrower, the slides can be grouped closer together such that the entire footprint of the autostainer has been reduced.

Autostainer Control and Programming

As stated in the previous section, the autostainer **100** is controlled by a personal computer system **190**. In one embodiment, the personal computer system **190** is a standard IBM compatible personal computer system running the Windows 95 operating system. The personal computer system **190** stores an autostainer control program **170** that is run when a user wishes to operate the autostainer **100**.

The autostainer control program **170** is a sophisticated control program that implements many security, autoprogramming, control, and logging features. To fully describe the autostainer control program **170**, this document will step through a sample use of the autostainer **100**.

Autostainer Control Program Initialization

When a user first runs the autostainer control program **170**, a sign-in screen is displayed as illustrated in **Figure 6**. The user enters a factory preloaded user name and password. After the factory preloaded user name and password have been entered, an option screen is displayed as illustrated in **Figure 7**.

The option screen displays a set of functions that the user may select such as programming the autostainer for a run (Program **710**), initializing the autostainer control program (Initialize **720**), cleaning the autostainer (Clean **730**), signing off (Sign Off **740**), and displaying help information (Help **750**). To initialize the autostainer control program **170**, the user selects Initialize **720**.

After selecting the Initialize **720** button on the options screen, the Initialize screen is displayed as illustrated in **Figure 8**. The initialization screen allows the user to enter information about the institution that will be using the autostainer in an institution information area **810**. Below the institution information area **810** is a staff information area **820**.

The staff information area **820** allows an entry to be created for each user that will use the autostainer **100**. The staff information area **820** allows both doctors and technologists to be entered. Each user entry includes a user name, a user password, and a security level. The user name and password are used during the sign in process. The security level is used to limit access to features of the autostainer control program.

Finally, the Initialize screen allows a few autostainer operation parameters to be set. In the embodiment of **Figure 8**, the parameter area **830** allows the user to specify the default reagent volume amount, the default reagent drop zone, and the number of runs allowed between cleanings.

The default reagent volume specifies the amount of reagent that will be used for all steps in any staining protocol. However, the default reagent volume can be overridden by specifically programming a different amount, as will be described later. The default reagent drop zone specifies the default location where reagent will be applied to the slides. The default reagent drop zone can be overridden on the Slide Layout Map screen of **Figures 19** and **20**, as will be described later.

The number of slides allowed between cleanings specifies how many times the autostainer may be used between maintenance cleanings. When the specified number of slides have been treated, a user will be notified that a cleaning cycle should be run at the Options screen.

Creating a Staining Run

To run the autostainer, a user signs in with his or her user name and password, as previously described with reference to **Figure 6**. Then, at the Option screen displayed in **Figure 7**, the user selects the Program button **710**. After the selecting the Program button **710**, a blank Program Staining Run screen is displayed as illustrated in **Figure 9a**.

The Program Staining Run screen is the central screen used to program a staining run. The Program Staining Run screen displays a grid of the steps that will be performed on each slide. The rows of the grid list the slides that will be stained. The columns of each row in the grid contain the patient name and case number, the doctor name, and all the steps that will be performed on that slide (row). The list of steps that will be performed on a slide, or groups of slides, are referred to as a "protocol."

Several pull-down menus are available on the top of the program staining run screen, including "File" and "Edit." The File pull-down menu allows the user to create a new staining run program, open an old staining run program, save the current staining run program, and print the current staining run program. The Edit pull-down menu displays a list of all the available reagent categories that can be edited. To edit a reagent, the user selects the reagent category from the Edit pull-down menu and then an appropriate Edit reagent list screen will be displayed. The editing of reagents will be explained later. The Edit pull-down menu also lists a "Detection Kit" item. If the Detection Kit item is selected, then the Detection Kit Lot Maintenance screen is displayed. The Detection Kit Lot Maintenance screen allows detection kits consisting of two or more reagents to be created.

Also available at the top of the program staining run screen is a "Copy" function. One or more steps in a protocol can be selected using the cursor control device, and then the "Copy" function can be used to copy the steps. The user can then move the cursor to another slide row and "Paste" the steps into that slide's protocol. Thus, by cutting and pasting similar steps, the programming time is decreased.

Beneath the grid of slide and protocol information are six buttons for accessing additional programming features. The Slide Information button **910** moves the user to a Slide Information screen in order to enter new or edit existing patient information. The Protocol Template button **920** moves the user to

a Protocol Template Design screen, where a new staining protocol template can be created or a stored protocol template retrieved. The Next button **930** is selected when the user is satisfied with the information in the Program Staining Run screen and wishes to start the staining run. The Print button **940** request the user to indicate if he or she wants a hard copy printout of the programmed staining grid that is currently displayed, or an immunohistochemical report (IHC), as illustrated in **Figure 9b**. The user simply selects the hard copy that is desired. The Exit button **950** returns the user to the Option screen as illustrated in **Figure 7**. If the program has been changed, the user is presented with the option of saving the program. The Help **960** button displays context sensitive help information.

The general procedure for programming a staining run is as follows: (1) enter the slide information for each slide; (2) select an existing or create a new protocol for staining run; (3) select the reagents that will be used in the staining run; and (4) load the slides and reagents and start the run. Each step merits its own discussion.

1) Entering Slide Information

To enter patient information for a staining run, the user selects the Slide Information button **910** from the Program Staining Run screen of **Figure 9a**. This moves the user to the Slide Information screen, as illustrated in **Figure 10**.

The Slide Information screen has input areas to allow the user to enter a patient name, a patient case number, the number of slides for that patient, and the doctor that requested the slides. After entering this information for a first patient, the form is cleared and the user can enter information for a next patient. The four buttons on the bottom of the Patient Information screen are used to perform various operations.

The Delete button **1020** is used to delete a patient entry or case entries. The user can delete a patient entry using the patient selector arrow **1011** to select a particular patient name, and then click on the Delete button **1020** to delete the selected patient entry. The user can delete a particular case for a patient entry using the patient selector arrow **1011** to select a particular patient name, then using the case selector arrow **1081** to select a particular case number, and then click on the Delete button **920** to delete the selected case.

The Cancel button **1030** allows the user to cancel all the entered patient information. When a user selects the Cancel button **1030**, the user returns to the Program Staining Run screen and none of the entered patient information is saved.

The Help button **1040** can be selected to receive context sensitive help information. Thus, the Help button **1040** displays help information about the Slide Information Screen.

After entering all the desired patients, the user selects the Finish Entry button **1010** to return to the Program Staining Run screen with the new patient information displayed. After entering all the patient information, the next step is to select an existing or create a new protocol for staining run. Thus, from the Program Staining Run screen the user selects the Protocol Template button **920**.

2) Creating A New Or Accessing An Existing Protocol Template

To select a protocol template for a staining run, the user selects the Protocol Template button **920** from the Program Staining Run screen. This moves the user to the Protocol Template Design screen as illustrated in **Figure 11**.

The Protocol Template Design screen of **Figure 11** is divided into two vertical columns. The left column is the Protocol Element column **1110**. The Protocol Element column **1110** lists the various steps that can be used to create a protocol. The right column is the Protocol Outline column **1120**. The Protocol Outline column **1120** lists the steps that have been selected for the current protocol.

The Protocol Template Design screen enables the user to create staining protocol templates to be used in the staining runs. Protocol templates can be created and stored for future use. To create a protocol template, the user selects protocol steps from the Protocol Element column **1110** and moves them to the Protocol Outline column **1120**.

The available protocol steps include: Endogenous Enzyme Block, Protein Block, Primary Antibody (and Pretreatment), Detection Kit, Secondary Reagent, Tertiary Reagent, Labeled Polymer, Substrate-Batch, Substrate, Auxiliary, Switch, and Rinse Buffer. The specific reagents used during reagent steps are assigned to each slide from the Program Staining Run screen, as will be described in the next section.

The Rinse Buffer step should be programmed between all protocol template steps to remove reagents from the slides between the staining run steps. The default Rinse Buffer step can be replaced by a blow step by clicking on the Rinse Buffer step droplet icon on the Program Staining Run screen with the right mouse button. This replaces the droplet icon with a wind icon, indicating a blow step.

The Substrate-Batch Protocol step allows the use of unstable substrates that need to be prepared immediately prior to application. The Substrate-Batch Protocol step splits the staining run into two phases: a first phase prior to the application of the unstable substrate, and a second phase batching all the steps starting with the unstable substrate application. The autostainer will stop after all the steps in the first phase and beep to indicate that the substrate should be prepared. The user then prepares the substrate and loads it into a designated position in the reagent rack. After the user has placed the unstable substrate into the designated position in the reagent rack, the user prompts the autostainer to continue the staining run.

The Switch step allows a user to indicate the switching of waste from one container to another. The Switch step is primarily used to separate hazardous waste from nonhazardous waste. A protocol template containing a Switch step switches from the primary (nonhazardous) waste system to a secondary (hazardous) waste system. On the Program Staining Run screen, the first Switch step will be displayed as a skull and crossbones to indicate a switch to the secondary (hazardous) waste system. The next Switch step will be displayed as a flower icon to indicate a switch to the primary (nonhazardous) waste system. Accordingly, subsequent switch steps alternate between the secondary (hazardous) waste system and the primary (nonhazardous) waste system. Switch steps must always be preceded by a rinse step.

As illustrated in **Figure 11**, the Protocol Template Design screen has the following function buttons: New Template **1140**, Get Template **1145**, Use Template **1160**, Delete **1130**, Reagent Volume **1123**, Save **1150**, Cancel **1170**, and Help **1180**. The New Template **1140** button clears the Protocol Outline column **1120** such that a new template may be created. The Get Template **1145** button displays a file requester box such that an existing template may be fetched. The Use Template **1160** button installs the protocol template displayed in the Protocol Outline column **1120** and returns to the Program Staining Run screen. Delete **1130** deletes a highlighted step from the Protocol Outline column **1120**. The Reagent Volume **1123** button assigns a reagent dispense volume to a highlighted step (or all the steps if a specific step is not highlighted) in the Protocol Outline column **1120**. The Save **1150** button saves the protocol template currently displayed in the Protocol Outline column **1120** into a file. The Cancel button **1170** allows the user to cancel all the entered information and returns the user to the Program Staining Run screen. The Help button **1180** can display context sensitive help information.

After selecting the Save **1150** button, the Use Template **1160** button, or the Cancel button **1170**, the user is returned to the Program Staining Run screen.

3) Selecting Reagents Used in the Staining Run

When the user returns to the Program Staining Run screen after selecting a protocol template, the first reagent step to be programmed will be flashing. There are two different ways of assigning reagents to the slides. The first method is to edit the reagents for a slide by selecting the slide. The second method is to select a reagent box on the Program Staining Run screen and an appropriate reagent list will be displayed such that a reagent may be selected.

To edit an individual slide, a user can select a slide tile and then click on the "Edit Slide" item displayed at the top of the reagent list. This brings up the Edit Individual Slide Reagent Window. For example, **Figure 12** illustrates the Edit Individual Slide Reagent Window for the Endogenous Enzyme Block of Slide 1. To select a reagent, the user can use the down arrow **1213** in the reagent name field to select the desired reagent. **Figure 13** illustrates how the Edit Individual Slide Reagent Window appears after the H_2O_2/N reagent has been selected.

Using the Edit Individual Slide Reagent Window, slide specific edits can be made. No edits made on the Edit Individual Slide Reagent Window will affect the reagent file. However, after the user selects the "OK" button **1210**, the user will be asked if he or she wants the same reagent applied to all the unprogrammed slides, as illustrated in **Figure 14**. If all or most of the slides are undergoing the same treatment, the user should select the "yes" button **1420** such that the autostainer program fills in the selected reagent for the same step in the remaining unprogrammed slides. If the majority of the slides have different protocols, the user should select the "no" button **1430**. The remainder of the reagents for the slide can be edited in the same manner.

The other method of editing reagents is to select a particular reagent tile from the Program Staining Run screen grid. This will bring up an appropriate list of reagents that may be selected. For example, **Figure 15** illustrates a Detection Kit tile for slide 3 highlighted such that an appropriate list of Detection Kits is displayed in a pop-up window **1510**. The user simply selects the desired Detection Kit from the pop-up window **1510**. Note that one of the Detection Kits in the list is "None" so the tile may be cleared.

After selecting a reagent, a window will ask the user if the same reagent should be assigned to the remaining unprogrammed slides, as explained above.

The user programs all of the reagent steps using the two methods described above. To reduce the work involved, the user can use the "Copy" command from the menu to copy protocol and reagent information from slides that have already been programmed into unprogrammed slide rows.

The autostainer of the present invention includes a compatibility check feature to prevent incompatible reagents from being used on the same slide. In a present embodiment there are two compatibility tests performed, although more can be added in future versions. The first compatibility check tests the species reactivity compatibility of the primary antibody and the secondary reagent used. The second compatibility check tests the compatibility rules dictated by the enzyme used in the detection system. The following chart summarizes the current compatibility rules:

Species Reactivity Compatibility Rules

First Compatibility Check: Species Compatibility

Reagent Type	Description	Compatibility Code
Primary Antibody	All monoclonal primary antibodies raised in mouse (e.g., mouse anti-human)	A
Primary Antibody	All polyclonal primary antibodies raised in rabbit (e.g., rabbit anti-mouse IgG)	B
Secondary Reagent	All secondary reagents (antibodies) compatible with monoclonal antibodies raised in mouse (e.g., biotinylated antimouse IgG)	A
Secondary Reagent	All secondary reagents (antibodies) reacting with polyclonal antibodies raised in rabbit (e.g., biotinylated antirabbit IgG)	B

Second Compatibility Check: Enzyme System Compatibility

Reagent Type	Description	Compatibility Code
Endogenous Enzyme Block	HRP-compatible	X
Endogenous Enzyme Block	AP-compatible	Y
Tertiary Reagent	HRP-labeled streptavidin	X
Tertiary Reagent	AP-labeled streptavidin	Y
Substrate	HRP-compatible substrates (i.e. DAB, AEC)	X
Substrate	AP-compatible substrates (i.e. Fast Red, New Fuchsin)	Y

When a user attempts to enter a reagent that is incompatible with a previously selected reagent, the Incompatible Reagent Warning Box is displayed, as illustrated in **Figure 16**. The Incompatible Reagent Warning Box asks the user if the incompatible reagent should be used. If the user selects "no" then an incompatible reagent is erased. If the user selects "yes", then the incompatible reagent remains.

To edit the actual reagents that are available for use, the user selects a reagent type from the Edit pull-down menu on the Program Staining Run screen. The Edit pull-down menu displays the following reagents that can have their parameters modified: Endogenous Enzyme Block, Protein Block, Primary Antibody, Pretreatment, Secondary Reagent, Tertiary Reagent, Labeled Polymer, Substrate, and Auxiliary. When the reagent type is selected, such as the Primary Antibody reagent, the user is moved to the Edit Reagent List screen, as illustrated in **Figure 17**.

At the top of the Edit Reagent List screen is a title **1710** that lists the type of reagent that can be displayed. In the example of **Figure 17**, the Collagen IV antibody of the Primary Antibody type of reagent is displayed. The remainder of the Edit Reagent List screen displays the relevant information for the particular reagent that is on the screen. The information includes: the reagent long name **1720**, the reagent short (10 character) name **1730**, a lot number **1740**, an expiration date **1745**, a compatibility code **1750**, and an incubation time **1760**. To edit the information, the user simply types in the desired field. In the particular case of the Primary Antibody reagent, the information about the corresponding pretreatment is also displayed including the pretreatment name **1781**, the pretreatment short (10 character) name **1783**, and the

incubation time **1785**. The information about the corresponding pretreatment can also be edited by typing in the desired field.

To select a different reagent of the type of reagent listed in the title **1710**, the user uses the name selector arrow **1721** or moves the cursor to the reagent long name field and presses the down arrow key until the desired reagent is displayed. The user then hits Enter to obtain the information about that particular reagent. To delete the reagent that is currently displayed, the user can select the Delete button **1795** at the bottom of the screen.

To return to the Program Staining Run screen, the user selects the OK button **1791**. To return to the Program Staining Run screen without saving the changes that have been entered the user can select the Cancel button **1793**. Context sensitive help is available by pressing the Help button **1797**.

4) Loading Reagents Used in the Staining Run

Once all the patient information has been entered, the desired slide protocols have been set up, and the desired reagents have been selected, the autostainer is ready to be operated. Thus, the user must physically load the slides and reagents. These steps will be described in the next section.

Autostainer Operation

After the patient information, the slide protocols, and the desired reagents have been entered, the Program Staining Run screen grid will appear as it does in **Figure 18**. To begin the staining operation, the user selects the Next button at the bottom of the Program Staining Run screen. The autostainer program will ask the user if the staining run program should be saved, as illustrated in **Figure 18**. After saving (or not saving) the programmed information, the user is moved to the Slide Layout Map screen, as illustrated in **Figure 19**.

The Slide Layout Map screen displays a grid of all 48 slides. Each slide is identified with the slide number, the primary antibody abbreviation, the primary antibody volume, and the case number.

Each slide also has a designation of where the reagent will be dispensed onto the slide. The non-frosted zone of each slide is divided into three dispense zones. The default dispense location is set on the Initialization screen of **Figure 8**. To change the dispense location for all the slides, the user can select any of the three zones on an "All Slides" icon **1910** in the upper left-hand corner. By toggling a zone of the "All Slides" icon **1910**, all the slides on the Slide Layout Map screen are affected. Furthermore, the

dispense location for individual slides can be set by toggling the three sections of the individual slide representation. **Figure 20** illustrates the Slide Layout Map screen after the top third of the "All Slides" icon **1910** has been toggled and several individual slides have been toggled.

The Slide Layout Map screen allows the user to make a final check of the staining run. If the user is not satisfied, the user can select the Cancel button **1930** to return to the Program Staining Run screen. The user can select the Print button **1940** to print the Slide Layout Map screen. The Help button **1950** displays context sensitive help information.

If the user is satisfied with the contents of the Slide Layout Map screen, then the user must load the slides into the autostainer as specified on the Slide Layout Map. After the user has loaded the slides, the user selects the OK button **1920** to proceed. After the user selects the OK button **1920** on the Slide Layout Map screen, the autostainer control program proceeds to calculate the most efficient dispensing pattern for performing the desired slide protocols.

Figure 21 illustrates a summary of how the autostainer control program calculates the most efficient dispensing pattern. Referring to **Figure 21**, at step **2105** the control program first groups together the slides in each step that have the same reagents and same incubation times. The same protocol scheduling number is assigned to groups with the same incubation time. An array is created for each group that contains an action time (the amount of time required to pick up and dispense reagents), a fixed time (the incubation time that follows the action time), and a variable time (10% of the fixed time) for each protocol step.

At step **2110**, a first group is selected as the "Currently Scheduled Array (CSA)." The control program then adds additional groups to the Currently Scheduled Array. At step **2115** an unscheduled group is selected. Next, at step **2120**, the selected group is fitted into the Currently Scheduled Array by adding to the action times within the fixed and variable times. **Figures 22a** through **22d** illustrate in detail how a group is added to a Currently Scheduled Array.

Step **2125** tests if the group fits into the Currently Scheduled Array. If it did not fit, the control program proceeds to step **2135** where it sees if it has tried to fit all the groups in the Currently Scheduled Array. If it has not tried to fit all the groups in yet, then it moves to step **2140** where another group is selected, and then back to step **2120** where it tries to fit that group in. If all groups have been tried,

then the control program moves to step **2150** where it moves to the next stage in the Currently Scheduled Array and then back to step **2120** where it tries to fit that group in.

Referring back to step **2125** when a group fits into the schedule, the control program then tests if all the groups have been scheduled. If all the groups have not been scheduled then the control program proceeds back to step **2115** to schedule another unscheduled group. If all the groups have been scheduled, then the process is done.

While the autostainer control program calculates, the control program displays the number of tries and the best time in a Run Time Calculation screen, as illustrated in **Figure 23**. When the autostainer control program is finished calculating the most efficient dispensing pattern, then a Run Time dialogue window is **2320** displayed. The Run Time dialogue window **2320** lists how long the staining run will take, how many times the probe will be washed, and how much buffer solution will be required for the staining run. The user clicks "OK" to proceed to the Reagent Layout Map screen.

Figure 24 illustrates the Reagent Layout Map screen of the autostainer control program. The Reagent Layout Map screen graphically displays a map of how the reagents should be loaded into the thirty-two vial reagent rack. Each vial is displayed with an alphanumeric rack position, the abbreviated reagent name, and the amount of reagent that is required.

The Reagent Layout Map screen includes several function buttons. When the user selects the Reagent List button **2410**, the reagent list appears as depicted in **Figure 25** and displays a detailed listing of the reagents used in the current staining run. Referring back to **Figure 24**, the Prime Pump button **2430** primes the pump by allowing buffer solution to flow out of the wash head. The Cancel button **2470** cancels the current staining run and returns to the Program Staining Run screen. The Slide Map button **2420** returns to the previous Slide Layout Map screen. The Print button **2460** prints out the reagent layout map. The Second Rack button **2440** displays a second rack of the reagents. The Second Rack button **2440** only appears if there are so many reagents required in the current staining run that a second reagent rack is required. The OK button **2450** starts the current staining run. The user selects the OK button **2450** only after all the required reagents have been loaded into the reagent rack.

After selecting the OK button on the Reagent Layout Map screen, the autostainer displays a Set Start Time Window as illustrated in **Figure 26**. The Set Start Time Window allows the user to select

when the autostainer will begin the staining run. If the user selects a large delay, the autostainer control program will request additional buffer solution to keep the slides moist. When the user selects the Start button **2610**, the autostainer control program begins the staining run. At this point the Run Log screen of **Figure 27** is displayed on the Control Program screen. The Run Log screen displays a detailed information log of the steps being performed along with a time stamp for each step. The Run Log screen displays the start time, the current time, and the projected finish time. To keep track of the current staining run, the Run Log screen displays the elapsed time, the projected remaining time, and the projected total run time.

The current staining run can be paused by selecting the "Emergency Stop" button **2710** the Run Log screen. This will cause an "Are You Sure" dialogue window **2715** to be displayed. The dialogue window **2715** allows the current staining run to be resumed or aborted.

During the staining run, each slide is processed exactly as the protocol has been programmed for that slide. To avoid contamination, the autostainer head moves in between the reagent vials and glass slides after reagent has been picked up.

As stated earlier, the reagent probe includes custom circuitry that allows the probe to sense liquid levels. During a staining operation, this feature is used to determine if there is enough reagent. When there is not enough reagent to complete a staining run, the autostainer control program stops and a dialogue window appears which informs the user about the problem. If the user responds to the dialogue window, then the autostainer control program will move the Z head assembly out of the way and will display a Reagent Layout Map screen showing the type, amount, and location of the reagent to be added. This allows the user to correct the problem. If the user does not respond within a minute, then the autostainer control program will use what reagent is available and continue operation. The autostainer control program will soon again stop and warn the user of the insufficient reagent. Again, if there is no response from the user, the autostainer control program will continue the staining run without the needed reagent. When there is insufficient reagent to satisfy the immediate need, the autostainer control program will skip the slides that need the missing reagent and note that in the run log.

While the autostainer control program is performing the staining run, the personal computer can be used to run other programs as long as the autostainer control program is being executed on a multitasking operating system such as Windows® 95 from Microsoft® Corporation of Redmond, Washington. In one embodiment, separate functions are used to program a staining run and to run a

staining run. Thus, while the staining run execution program is running, a user can execute the staining run programming function in order to program future staining runs.

After the staining run has completed, an "End Program Run" dialog box will be displayed and the computer will beep occasionally. At this point the user can print out a full copy of the program run log such that an Immunohistochemical Report can be created. The run information for any particular slide can be later recalled and used in conjunction with images of the stained slide captured with a CCD camera. Thus, a complete history of each slide will be available for analysis and diagnosis.

Stat Function

The Stat slide function of the autostainer allows the user to interrupt in-process staining of slides in order to initiate and stain one or more additional slides containing specimens that require immediate (stat) analysis, as disclosed in co-pending patent application Serial No. 09/483,248, which is expressly incorporated by reference herein in its entirety. The overall process of programming Stat slides in an in-progress staining run is schematically shown in FIG 28. During the staining run, the Increment Run Schedule Index, which refers to a counter that keeps track of which element in an array of pointers is the current pointer, is constantly updated. Each pointer points to another type of array containing pointers to link lists of actions that the instrument must perform in order to stain the slides. Incrementing the Run Schedule Index prepares the program to start processing the steps for the next sub-schedule and/or the addition of a slide or slide groups. This enables a user to determine if the schedule is interruptible when the user selects the Stat slide function.

In reference to FIG. 29, if the staining program that was already in progress when the Stat function was selected had also enabled the Stat function, the previous Stat function is disabled and the "New Program" and "Review Program" functions are enabled. If the Stat function had not been previously enabled, the "New Program" and "Review Program" functions are disabled. Upon initiation of the Stat function, the "Stat Slides" button displays the time remaining before the current program, in progress, can be interrupted and processing of the new Stat slides can be initiated.

FIG. 30 shows the "Timer Message" routine, which is displayed when the Stat function is enabled. This routine calculates the time until the next interruption point, converts it to hours and minutes, and displays it on the "Stat Slides" button. Other times are then subsequently updated, including the length of time that the staining run has been in process, the length of time until the current run is finished, the

beginning, projected completion, and total staining run time, and the current time. When both of the functions in FIGS. 29 and 30 are completed, the program returns to the routine in FIG. 28. When all the slides are in rinse buffer the user sees the prompt "Ready For Stat Slides", and must select whether he or she wishes to interrupt the current program to include the stat slides.

If the user selects "NO", or ten minutes elapse with no user response, staining of the pending slides continues. If the user selects "YES", the program then hides the Run Log and displays the Main Programming grid. The user can then begin programming the stat slides, following a programming procedure as previously described (Creating a Staining Run). The programming procedure includes functions of defining protocol templates and methods, changing reagent dispensing locations and volumes, and adding new reagents.

When the user has finished programming the added slides, the program then initiates several routines to group the pending and added slides according to identical or aligned protocols, and then schedules the Stat slides for the staining run. These routines are schematically illustrated in FIGS. 31 and 32A through 32G, with an option whether to complete processing of the Stat slides before, or concurrently with, the pending slides.

If Stat slides are added to the schedule, the program is restarted (Disable Delayed Start) and returns to the Begin Staining Run routine, shown at 1A in FIG. 28. If Stat slides are not added to the schedule, the program returns to the original schedule and continues staining slides from the point at which it was previously interrupted.

With reference to FIG. 31, beginning at 2B, the main grid is displayed and accepts programming for groups of slides, as previously described (Creating a Staining Run). If the programming that has been selected is compatible with the current protocol, now interrupted, the program inquires whether the user wishes to complete the Stat slides first by displaying "Finish Stat Slides First?" or another similar query. If the user wishes to complete staining of Stat slides first, or if the protocols are not compatible with any of the current protocols, the program then adds null steps, both before any currently pending groups and after the newly added Stat slide treatment steps, to allow the Stat slide groups to be completed before any other slide groups. If the user does not wish to complete the Stat slide groups first, the Stat slide groups are merged with the current slide groups in a combined program, to stain both the pending slide groups and the

Stat slide groups. The program then schedules the staining run, shows the assignment of reagents for the run reusing the reagents racks for vial assignments, and returns to the routine shown in FIG. 28 at 2B.

FIG. 32A shows further details of a staining run. To schedule a staining run, the staining steps are divided into sub-schedules, each sub-schedule terminating with all slides incubated in rinse buffer. The slides to undergo the same staining protocols are then grouped. The program calculates the total staining time for each sub-schedule, which is then added to the list of possible "interrupt" times. The program continues this process for each group. Once all the sub-schedules are built, the program then returns to the next function (Reagent Vial Allocation, adding the volumes of reagents required to complete the staining run, and assigning the volumes to reagent vials, as previously described (Creating a Staining Run)).

FIG. 32B shows how the sub-schedules are built. The sub-schedules are divided into "laps." In the first lap, the slide groups are ordered numerically. Once the first lap is completed, the second lap is initiated, in which the slide groups are ordered by incubation time, with the longest incubation time first, for the specific desired staining protocol. Once the second lap is completed, the third lap is initiated, in which the slide groups are ordered by treatment time, with the shortest treatment time first, for the specific desired staining protocol. Once the third lap is completed, the fourth lap is initiated, in which the slide groups are ordered by the difference of incubation time minus the treatment time (incubation time - treatment time), with the greatest difference first. With reference to FIG. 32B, after the fourth lap, subsequent laps start with the best schedule from the first four laps and rotate the order of the slide groups by moving the first group to the end and shifting the other groups up one.

For each lap, the steps required to treat the first group of slides are assigned as the initial entries in the Current Scheduled Array (CSA). The program then selects the next unscheduled slide group and attempts to add it to the schedule. If the group does not fit into the schedule, and if all the groups were not yet tried, the next group is tried. If all of the groups were tried in the schedule, there is a shift to the next stage in the Current Scheduled Array and the scheduling process is repeated. The effect of shifting to the next stage usually results in groups that have already been scheduled being incubated and rinsed before the next group of slides is treated. If the group does fit into the schedule, and if all the slide groups are not accounted for nor scheduled, the program then repeats the procedure until all the slide groups are accounted for.

Once all the slide groups are scheduled, including those groups that contain additional or Stat slides, the program then compares staining times for all the groups to the best-known time, and selects the best schedule. For each ordering of groups, an alternate order is created by combining groups with the same reagent. "Combining groups" means making them consecutive, although not necessarily treating them as the same group. The first group of a combined group consist of slides from the original order of the groups, that is, slides that were pending at the point of interruption. Subsequent groups in the combined groups are selected as those using the same reagent, regardless of their positions in the original order. FIG. 32C, beginning at 2A, shows the routine to achieve the Current Scheduled Array by adding a slide, or slide group, to the schedule. The schedule starts with the first group from the ordered list. Subsequent groups are added to the schedule, where they will fit without violating the limits of incubation times for all groups already scheduled. If the reagents for the next group to be added are different, the program adds time required for cleaning the reagent probe to accommodate the new reagents ("probe clean time"), and then the program checks whether the new group action time (a), is less than or equal to the current schedule fixed time F (the incubation time that follows the action time). If the new group action time (a) is not less than or equal to the current schedule fixed time, the program then checks whether the new group action time (a) is less than or equal to the current schedule fixed time (F) plus current schedule variation time (V). If the new group action time (a) is not, the program returns the result NO, because it does not fit, and returns to 3B in FIG. 32B. If the new group action time (a) is less than or equal to the current schedule fixed time (F) plus the current schedule variation time (V), the current schedule fixed time (F) is set equal to zero. Alternatively, at the outset, if the new group action time (a) is less than or equal to the currently schedule fixed time (F), the currently schedule fixed time (F) becomes equal to itself minus the new group action time (a), and the program continues.

At this point, the current schedule action time (A) is recalculated by adding the new group action time (a) to the existing current schedule action time (A). The program indicates where to add the step to accommodate the Stat slide group after the Current Scheduled Array. If the program is at the end of a particular slide group step list (i.e., the list of functions to perform), or is at the end of a Current Scheduled Array, the routine beginning at 5G in FIG. 32G, is initiated. If not, the routine beginning at 3C in FIG. 32D is initiated.

With reference to FIG. 32D, beginning at 3C, the program first questions whether the new group fix time (f) is greater than the current schedule fixed time (F) plus the current schedule action time for the next stage (A1). If it is not, the program then queries whether it is at the end of a Current Scheduled Array and, if so, goes to the function beginning at 5G in FIG. 32G. If it is not at the end of a Current Scheduled Array, the program then queries whether the accumulated current variable time (Va) is greater than or equal to the current schedule variable time (F) plus the current schedule action time for the next stage (A1) minus the current schedule variable time (V) for the new slide group. If it is not greater than or equal to this number, the program then follows the function shown beginning at 4E in FIG. 32E. If it is greater than or equal to this number, the program then takes the current schedule variable time (V) from the prior stages and adds it to the new group variable time (v). The program (1) sets the temporary current schedule fixed time (TF) to the current schedule fixed time (F); (2) sets the current schedule action time for the next stage plus motion time (am) by adding the current schedule action time for the next stage (A1) to the motion time, (3) calculates the current schedule fixed time (F) as a function of the maximum of the current schedule fixed time and current schedule action time for the next stage plus motion time (am), and (4) calculates the current schedule variable time (V) as a function of the minimum of the temporary current schedule fixed time (TF) plus the current schedule variable time (V) minus the current schedule fixed time (F), and the new group fixed time (f) plus the new group variable time (v) minus current schedule action time for the next stage plus motion time (am) minus the current schedule fixed time (F). The program determines whether the new group variable time (v) is less than zero. If it is, the program then returns the results NO, indicating that it did not fit the schedule, and returns to 3B in FIG. 2B. If it is not, the program then initiates the events beginning at 2A in FIG 32C.

If the new group fixed time (f) is greater than the current schedule fixed time (F) plus the action time for the next stage (A1), as shown beginning at 3C in FIG. 32D, the program then queries whether the new group fixed time (f) is greater than the current schedule fixed time (F) plus the current schedule action time for the next stage (A1) minus the current schedule variable time (V). If it is not greater, the program then follows the function beginning at 3D, previously described. If it is greater, the program then sets the new group variable time (v) equal to the new group variable time (v) minus the current schedule variable time (V). The program queries whether the new group variable time (v) is less than zero. If it is, the program resets (1) the current schedule variable time (V) equal to V plus the new group variable time (v), (2)

the current schedule fixed time (F) equal to F plus the new group fix time (f), and (3) the new group variable time (v) equal to zero. At this point, or if the new group variable time (v) is not less than zero, the program sets the accumulated current variable time (Va) by adding Va plus the current schedule variable time (V), and sets the new group fix time (f) equal to (f) minus the current schedule variable time (F) plus the action time for the next stage (A1). The program then skips to the next stage in the Current Scheduled Array.

If the accumulated current variable time (Va) is not greater than or equal to the current schedule fixed time (F) plus A1 minus the current schedule variable time (V), the program then initiates the routine beginning at 4E in FIG. 32E. The temporary current schedule variable time (TV) is set as the current schedule variable time (V). If the current schedule fixed time (F) is greater than the new fixed time (f) plus the new group action time for the next stage plus motion time (am), and if F is also greater than f plus am minus the new group variable time (v), then (1) the temporary current schedule fixed time (TF) is set equal to the current schedule fixed time (F) minus the new fixed time (f), (2) F is set equal to f, and (3) the temporary current schedule variable time (TV) is reset to TV minus the new group variable time (v). If TV is less than zero, (1) v is reset to v plus TV, (2) f is reset to f minus TV, (3) TV is set equal to zero, (4) the current schedule variable time (V) is set equal to the new group variable time (v), and (5) the accumulated variable time (Va) is reset to Va plus v. If TV is not less than zero, then steps (4) and (5) are followed. A new Current Schedule Array stage is then inserted and (1) the current schedule action time (A) is set equal to the new slide action time (a), (2) F is reset equal to TF minus a, and (3) V is reset to equal TV.

With reference to FIG. 32E when F is not greater than f plus am, and the input is at the end of the Slide Step List or Current Schedule Array (End of Slide Step List or CSA), the routine beginning at 5G in FIG. 32G is initiated. If it is not at the end of the Slide Step List or Current Schedule Array, and Va is not equal to or greater than F minus am, and there are no skipped or added stages, then the routine beginning at 3D in FIG. 32D is initiated. If there are skipped or added stages, then the routine beginning at 2B in FIG. 31 is initiated.

If Va is greater than or equal to F minus am, then the current schedule variable time (V) from the inserted stages is added to the new group variable time (v). This is followed by (1) resetting TF to equal F, (2) resetting F to equal the maximum of the function of the new group fixed time (f) and F minus am, and (3) resetting V to equal the minimum of the function of the new group fixed time (f) plus v minus F, and TF plus V minus am minus F. Earlier in routine 4E, if F is not greater than f plus am minus v, then

previous steps (1), (2) and (3) are performed. If the new group variable time (v) is less than zero, then the program returns the result NO, because the group did not fit, and returns to routine 3B in FIG. 32B. If the new group variable time (v) is not less than zero, then the program (1) shifts to the Next Slide Step and Current Schedule Array stage, and (2) initiates the routine beginning at 5F in FIG. 32F.

With reference to the routine beginning at 5F, the initial query is whether the new group fixed time (f) is less than the current schedule action time (A). If the answer is yes, then the query is whether the new group fixed time (f) is less than the current schedule action time (A) minus the new group variable time (v). If the answer to this second question is yes, then the program returns the result NO, because the group did not fit, the program returns to the routine beginning at 3B in FIG. 32B. If it is not, or if the answer is no to the question at the beginning of 5F, then (1) the new group variable time (v) is set equal to the new group fixed time (f) minus the current schedule action time, (2) the new group fixed time (f) is set to zero, and (3) the current schedule action time (A) is reset to A plus the new group action time for the next stage plus the motion time (am). The program then notes where to add the step before the Current Schedule Array and returns to the routine beginning at 2B in FIG. 31.

When the routine beginning at 5G in FIG. 32G is initiated, and the function is at the end of the Current Scheduled Array, then the array stage for each new slide is added (Add CSA Stage for Each New Slide Step). Specifically, the steps beginning at 2A in FIG. 32C, and beginning at 5F in FIG. 32F, are appended to their corresponding steps in the Current Schedule Array, a YES result is returned, and the routine returns to 3B in FIG. 32B. If it is not the end of the Current Schedule Array, then all new steps are added to the Current Schedule Array, a YES result is returned, and the routine returns to 3B in FIG. 32B.

The foregoing has described a method and apparatus for automatic tissue and cell preparation staining. It is contemplated that changes and modifications may be made by one of ordinary skill in the art, to the materials and arrangements of elements of the present invention without departing from the scope of the invention.

What is claimed is:

1. A computer program product comprising a computer usable medium having computer readable code embodied therein for automatically staining a plurality of slides each having a specimen thereon and contained on a slide rack, the computer usable medium comprising means selected from the group consisting of means for providing a rinse buffer, means for providing an unstable reagent, means for switching waste between a hazardous waste and a non-hazardous waste, means for blocking staining of an endogenous enzyme, means for blocking staining of a protein, means for providing a primary antibody, means for providing a secondary reagent, means for providing a labeled polymer, means for providing a detection kit, means for assigning a reagent to a slide, means for checking compatibility of reagents, means for locating at least one location on said slide for dispensing a reagent, means for efficiently dispensing a reagent to a plurality of said slides, means for proving a reagent layout map, means for providing an auxiliary function, means for staining a stat slide concurrently with or prior to said slides in process, and combinations thereof.

2. The computer program product of claim 1 wherein said means for providing an unstable reagent comprises a first phase prior to application of said unstable reagent and a second phase batching staining steps starting with application of said unstable reagent.

3. The computer program product of claim 1 further comprising stopping said autostainer after said first phase and alerting said user to provide said unstable reagent to said autostainer.

4. The computer program product of claim 1 wherein said means for switching waste is preceded by means to effect a rinse step.

5. The computer program product of claim 1 wherein said means for assigning a reagent to a slide is selected from the group consisting of selecting said slide and editing said reagent pre-selected for said slide, and selecting a list of said reagents and selecting a reagent from said list.

6. The computer program product of claim 1 wherein said means for checking compatibility comprises testing species reactivity compatibility of a primary antibody and a secondary reagent, and testing enzyme system compatibility.

7. The computer program product of claim 1 wherein said means for efficiently calculating reagent dispensing comprises

determining said slides in each step to be stained with the same reagents and for the same time;

grouping said slides into at least a first and a second grouping;

assigning a protocol scheduling number to said first grouping of slides;

creating an array for said first grouping of slides comprising an action time to withdraw and dispense reagent, a fixed time to incubate said slides with said reagent, and a variable time that is 10% of said fixed time; and

testing said second grouping of slides to determine if said second grouping of slides fits into said array; and

advancing to a subsequent stage in said array and then retrying testing said second grouping of slides of determine if said second grouping of slides fits into said array.

8. The computer program product of claim 7 further comprising building sub-schedules for said second grouping of slides.

9. A method of operating an autostainer comprising:

providing at least one first processing protocol for processing a plurality of first slides;

determining a first processing schedule for said plurality of first slides from said at least one first processing protocol;

processing said plurality of first slides according to said first processing schedule;

interrupting the processing of said plurality of first slides before completion of said first processing schedule;

specifying a second processing protocol for a second slide; and

determining a second processing schedule from said at least one first processing protocol and said second processing protocol; and

resuming the processing of said first plurality of slides and said second slides according to said second processing schedule.

10. The method of claim 9 wherein the step of determining said second processing schedule includes comparing the compatibility of said second processing protocol with said at least one first processing protocol.

11. The method of claim 9 further wherein the step of resuming the processing further comprises processing said second slide before processing said first plurality of slides.

12. The method of claim 9 wherein the step of resuming the processing further comprises processing said first plurality of slides and said second slide concurrently.

13. The method of claim 9 wherein the step of specifying said second processing protocol further comprises selecting a plurality of slide preparation steps using a graphical user interface.

14. The method of claim 9 further comprising, before the step of determining said second processing schedule, the steps of:

displaying reagent information for said second processing protocol; and

providing additional reagents appropriate for accomplishing said second processing schedule.

15. A computer program product comprising a computer usable medium having computer readable code embodied therein for interrupting the processing of pending slides by an autostainer and programming additional slides for processing using means to interrupt said processing of slides, means to select processing protocols for said additional slides, means to schedule processing of said pending and

additional slides to generate a processing schedule, and means to enable processing of pending and additional slides.

16. The product of claim 15 wherein said means to interrupt processing of pending slides comprises enabling a stat function and thereafter determining a time in said processing for processing said additional slide.

17. The product of claim 16 further comprising means for selecting whether to process additional slides prior to or concurrently with said pending slides.

18. The product of claim 15 wherein said means to select processing protocols for said additional slides comprises selecting methods and reagents for said additional slides.

19. The product of claim 15 wherein said means to schedule processing of slides comprises determining compatible processing protocols among the pending slides and additional slides; grouping slides for processing; forming sub-schedules for the slide groups; and determining a time to initiate processing from the sub-schedules.

20. The product of claim 15 wherein said means to enable processing of slides comprises processing said slides according to said processing schedule.

21. A computer program product for an autostainer comprising:

a first computer readable code operable to process a plurality of first slides according to a first processing schedule from at least one first processing protocol, a second computer readable code operable to interrupt said first processing schedule, a third computer readable code operable to select a second processing protocol for a second slide, a fourth computer readable code operable to generate a second processing schedule from said at least one first protocol and said second protocol, and a fifth computer readable code operable to enable processing of said plurality of first slides and said second slide according to said second processing schedule; and

a computer readable medium that stores said first, second, third, fourth and fifth computer readable codes.

22. The product of claim 21 wherein second computer readable code further comprises computer-readable instructions enabling a stat function.

23. The product of claim 22 further comprising a sixth computer readable code operable to select whether to process said second slide prior to or concurrently with said plurality of first slides, said computer readable medium further storing the sixth computer readable code.

24. The product of claim 21 wherein said third computer readable code further comprises computer-readable instructions for selecting a method and at least one reagent for said second processing protocol.

25. The product of claim 21 wherein fourth computer readable code further comprises:

computer-readable instructions for comparing said at least one first protocol and said second protocol;

computer-readable instructions for grouping slides according to the result of the step of comparing in a plurality of slide groups for processing;

computer-readable instructions for forming sub-schedules from said slide groups; and

computer-readable instructions for determining a time to initiate processing of said plurality of first slides and said second slide according to the sub-schedules.

26. An autostainer comprising

an automatic staining apparatus having capacity for a plurality of slides and dispensing reagents onto said slides, said autostainer responsive to a set of electrical commands, said plurality of slides comprising a first set of slides, a second set of slides, and at least one stat slide;

a computer system coupled to said autostainer for delivering said set of electrical commands; and

an autostainer control program executing a first set of programmable protocol steps for said first set of said slides, a second set of programmable protocol steps for said second set of said

slides, and a set of programmable protocol steps to interrupt said protocol steps for said first and second set of said slides and include said stat slide in said protocol.

27. The apparatus of claim 26 further comprising an autostainer protocol editor program, said autostainer protocol editor program for programming said first and said second set of programmable protocol steps for said first and said second set of said slides, respectively.

28. An apparatus for processing slides comprising:

a reagent rack for storing a plurality of different reagents;

a slide rack for holding a plurality of first slides; and

a robotic motion control system, said robotic motion control system having a probe for dispensing reagent from said reagent rack onto said first slides according to a first processing schedule, said control system adapted to interrupt the first processing schedule for adding a second slide to said slide rack and to calculate a second processing schedule for said plurality of first slides and said second slide.

29. The apparatus of claim 28 further comprising a control program for determining said first and said second processing schedules.

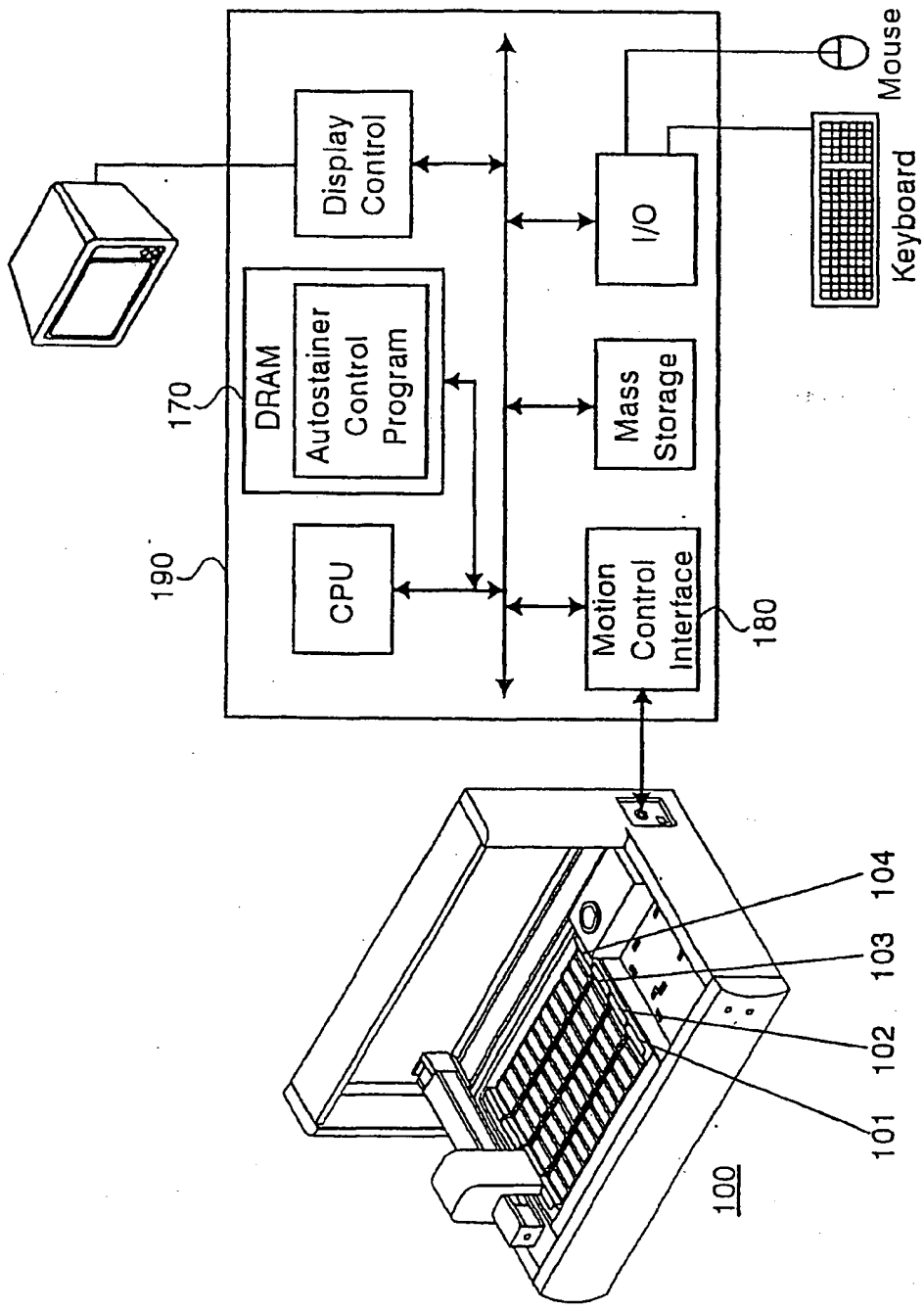
Display Control
I/O
Mouse
Keyboard
DRAM
Autostainer Control Program
170
Mass Storage
CPU
190
Motion Control Interface
180
100
101
102
103
104

Figure 1a

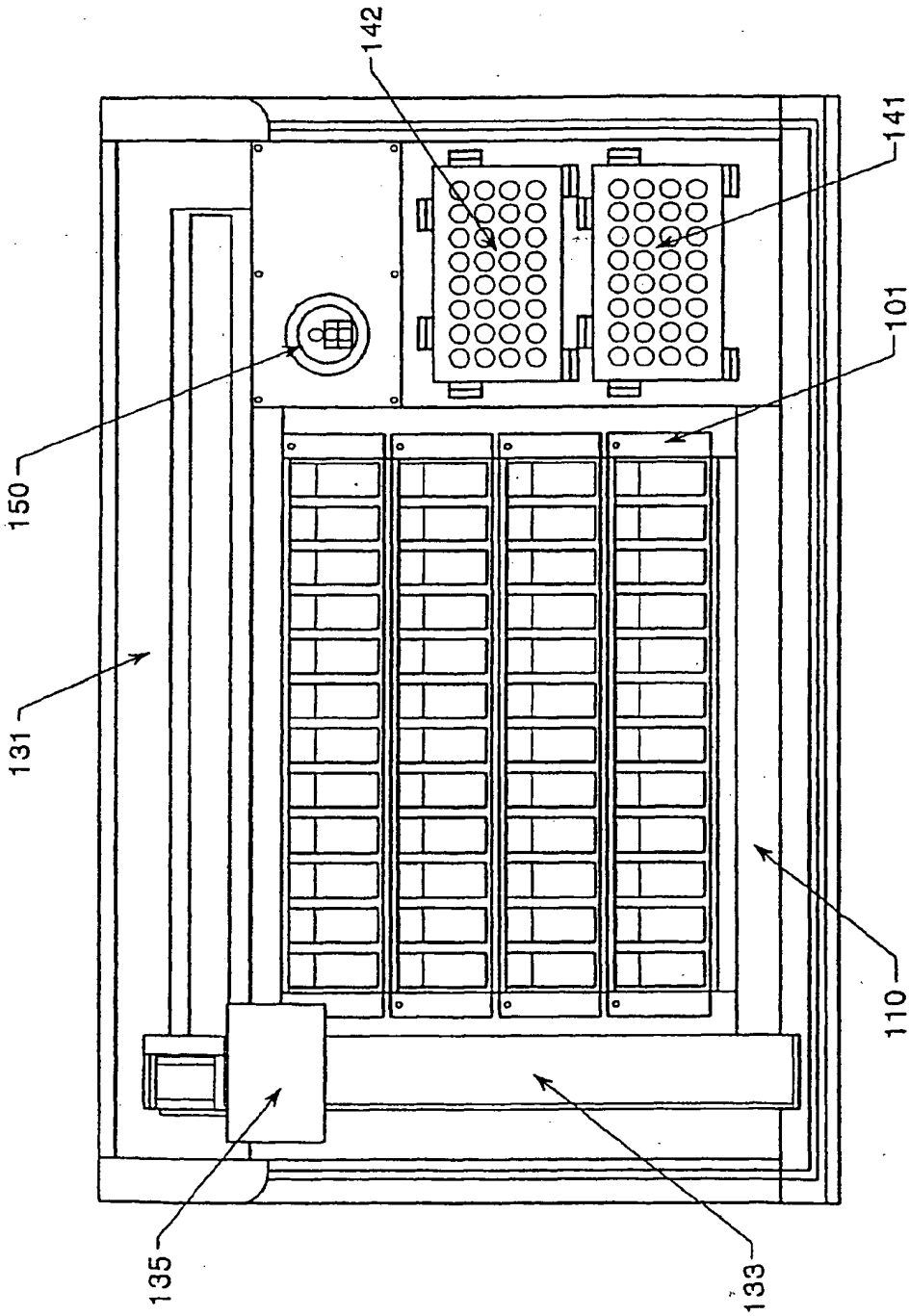

Figure 1b

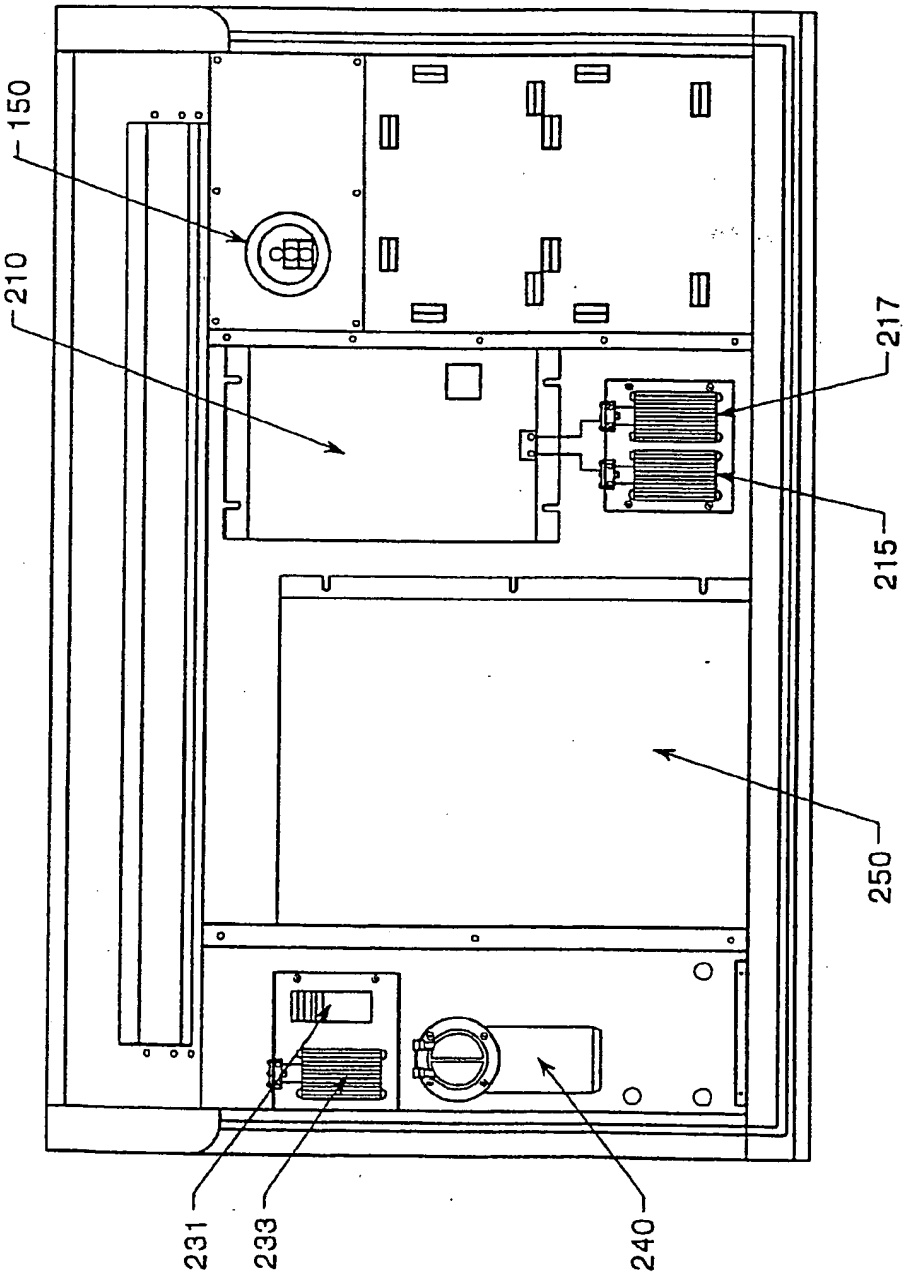

Figure 2

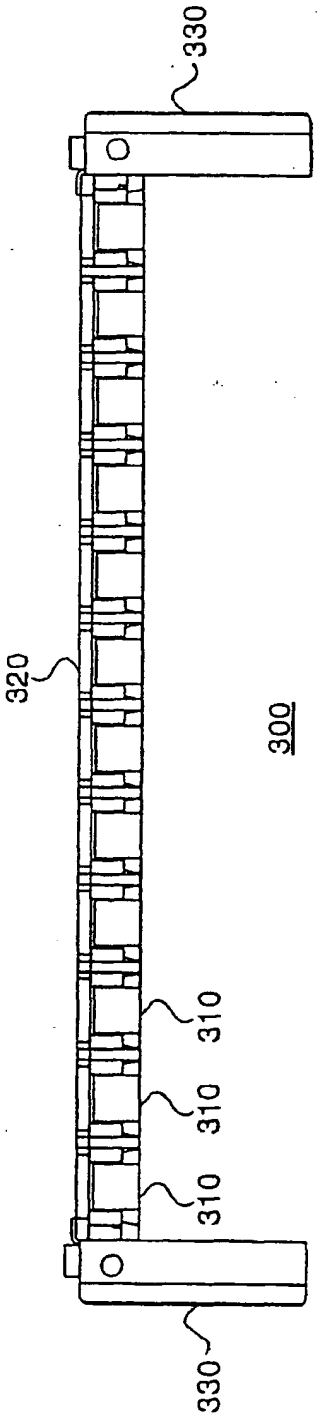

Figure 3a

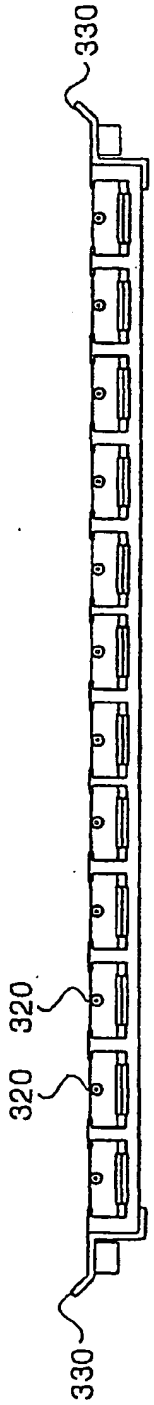

Figure 3b

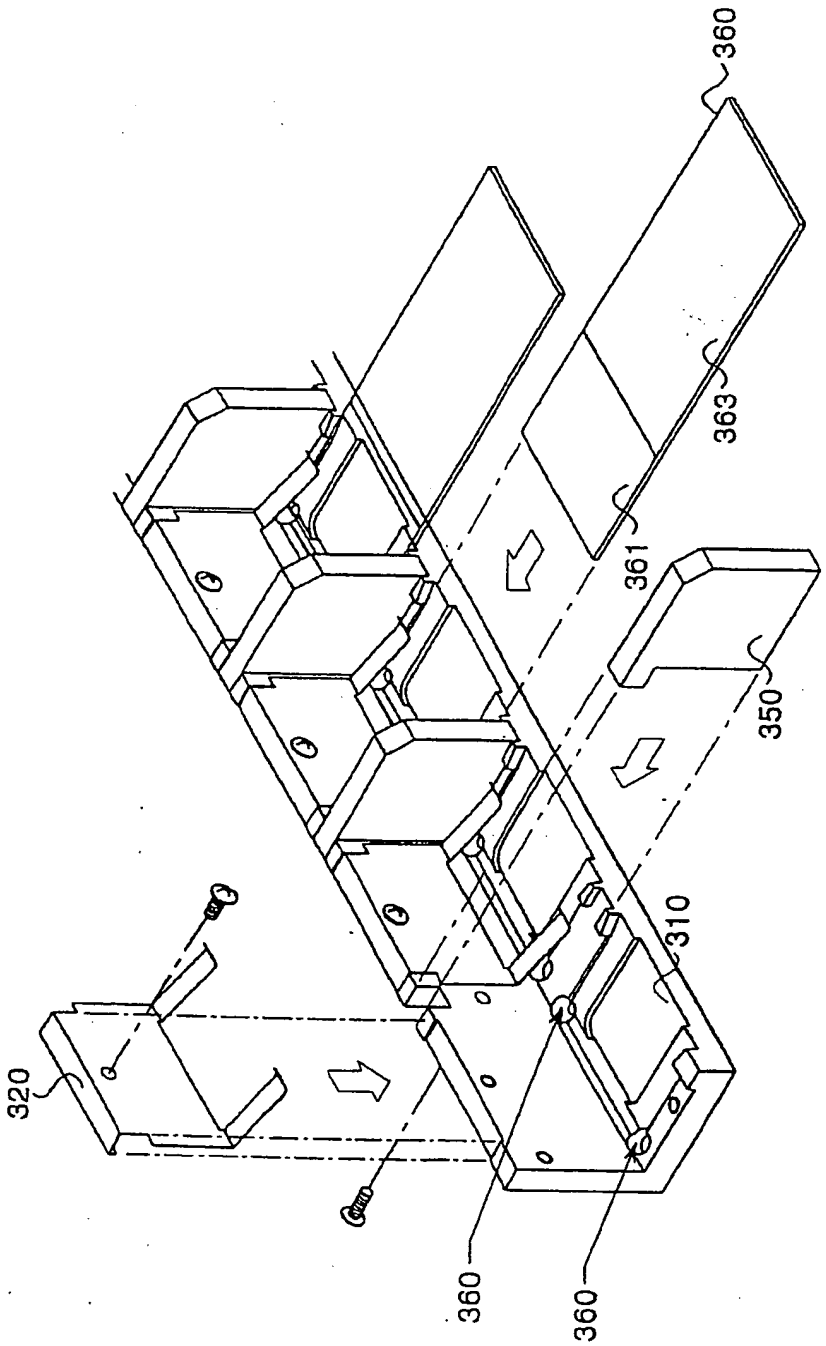

Figure 3c

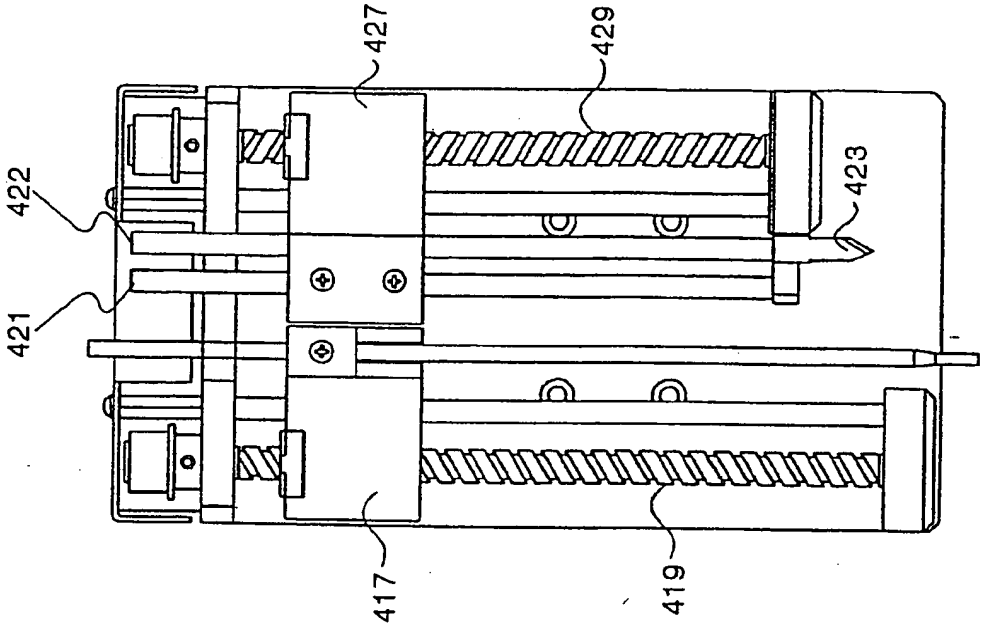

Figure 4b

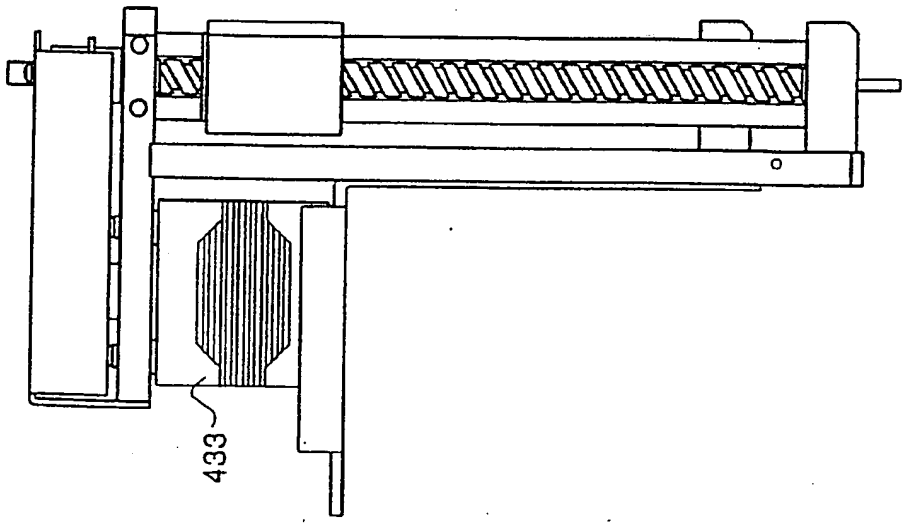

Figure 4a

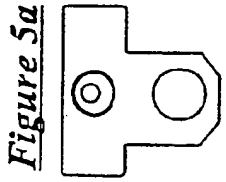

Figure 5a

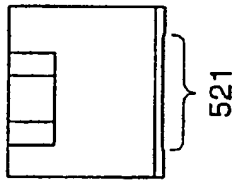

Figure 5c

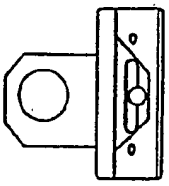

Figure 5f

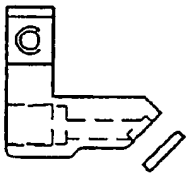

Figure 5b

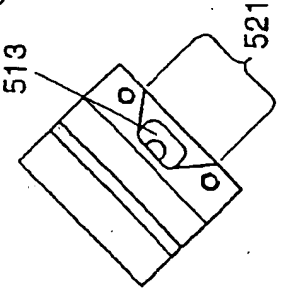

Figure 5e

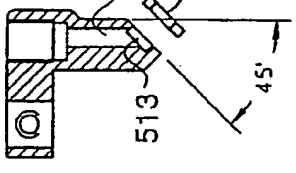

Figure 5d

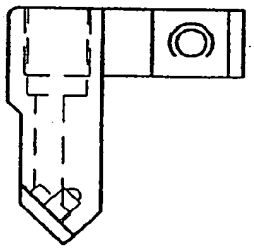

Figure 5g

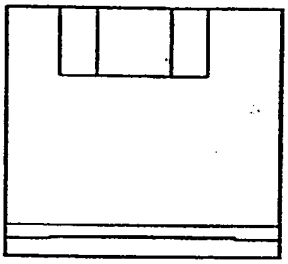

Figure 5h

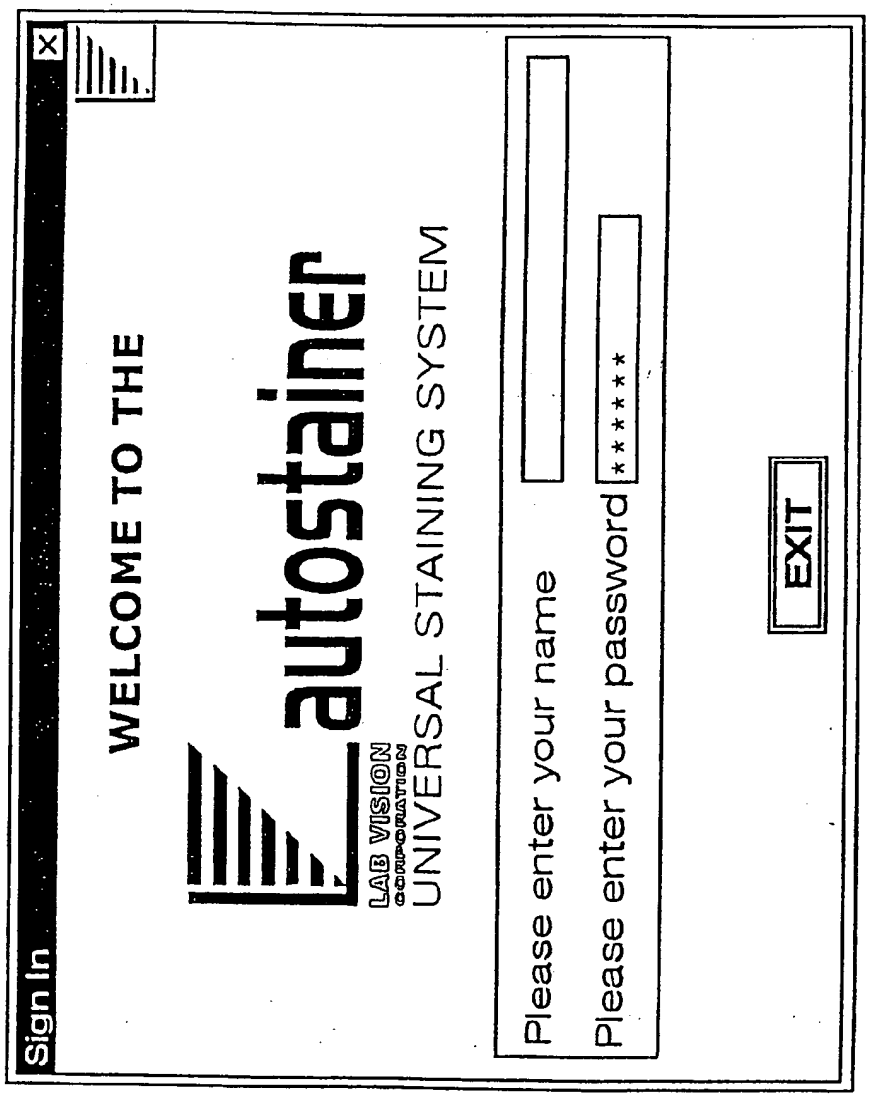
Sign In
WELCOME TO THE
autostainer
LAB VISION CORPORATION
UNIVERSAL STAINING SYSTEM
Please enter your name
Please enter your password
******
EXIT

Figure 6

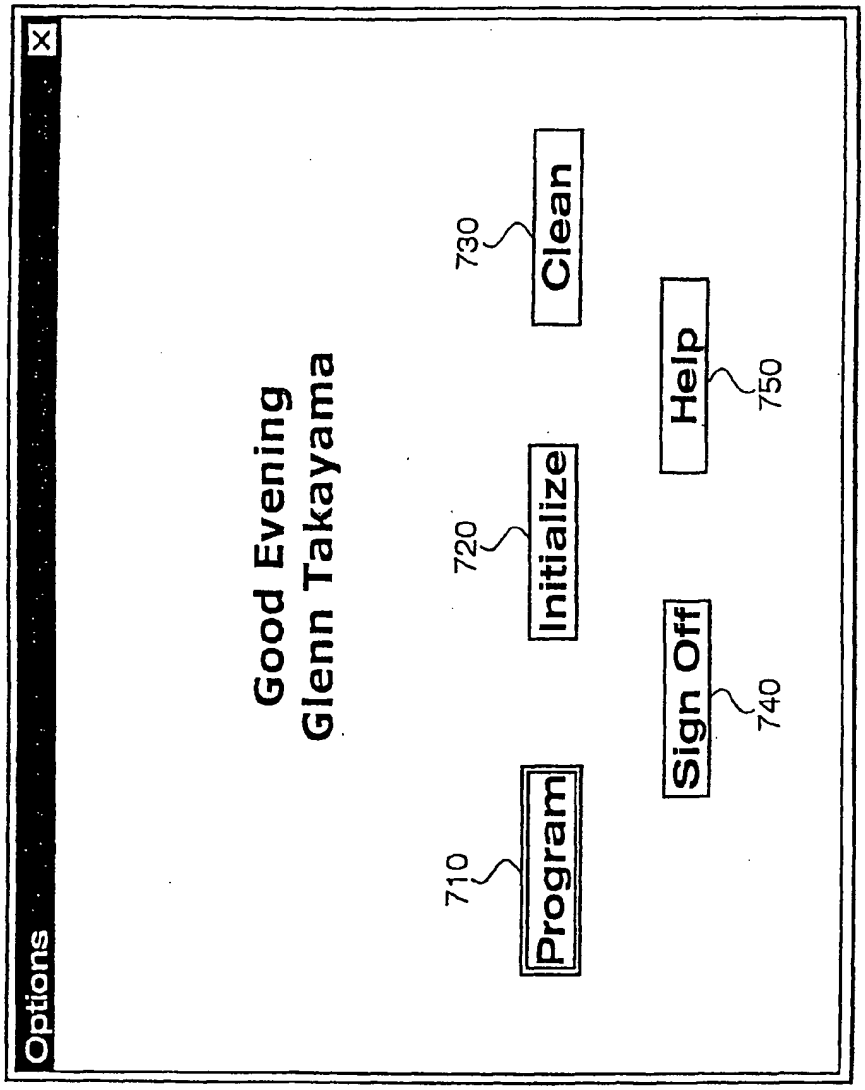
Options
Good Evening
Glenn Takayama
710
Program
720
Initialize
730
Clean
740
Sign Off
750
Help

Figure 7

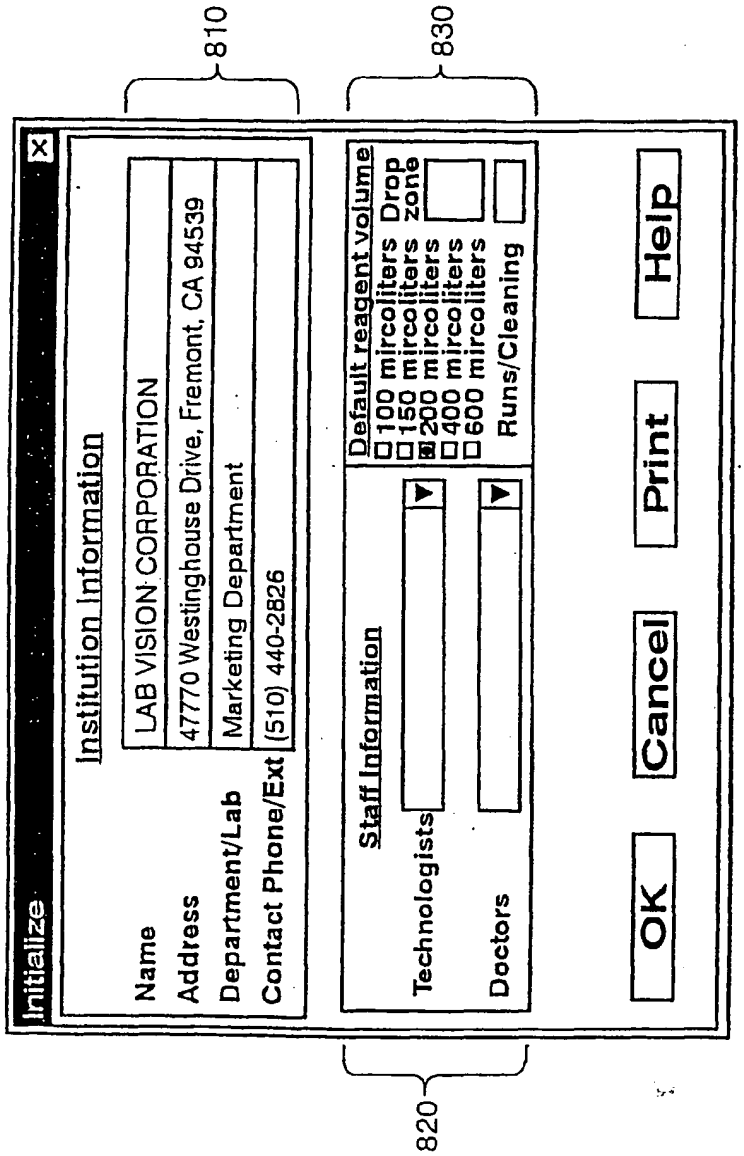
Initialize
Institution Information
Name
LAB VISION CORPORATION
Address
47770 Westinghouse Drive, Fremont, CA 94539
Department/Lab
Marketing Department
Contact Phone/Ext
(510) 440-2826
Staff Information
Technologists
Doctors
Default reagent volume
100 mircoliters
150 mircoliters
200 mircoliters
400 mircoliters
600 mircoliters
Drop zone
Runs/Cleaning
OK
Cancel
Print
Help
810
820
830

Figure 8

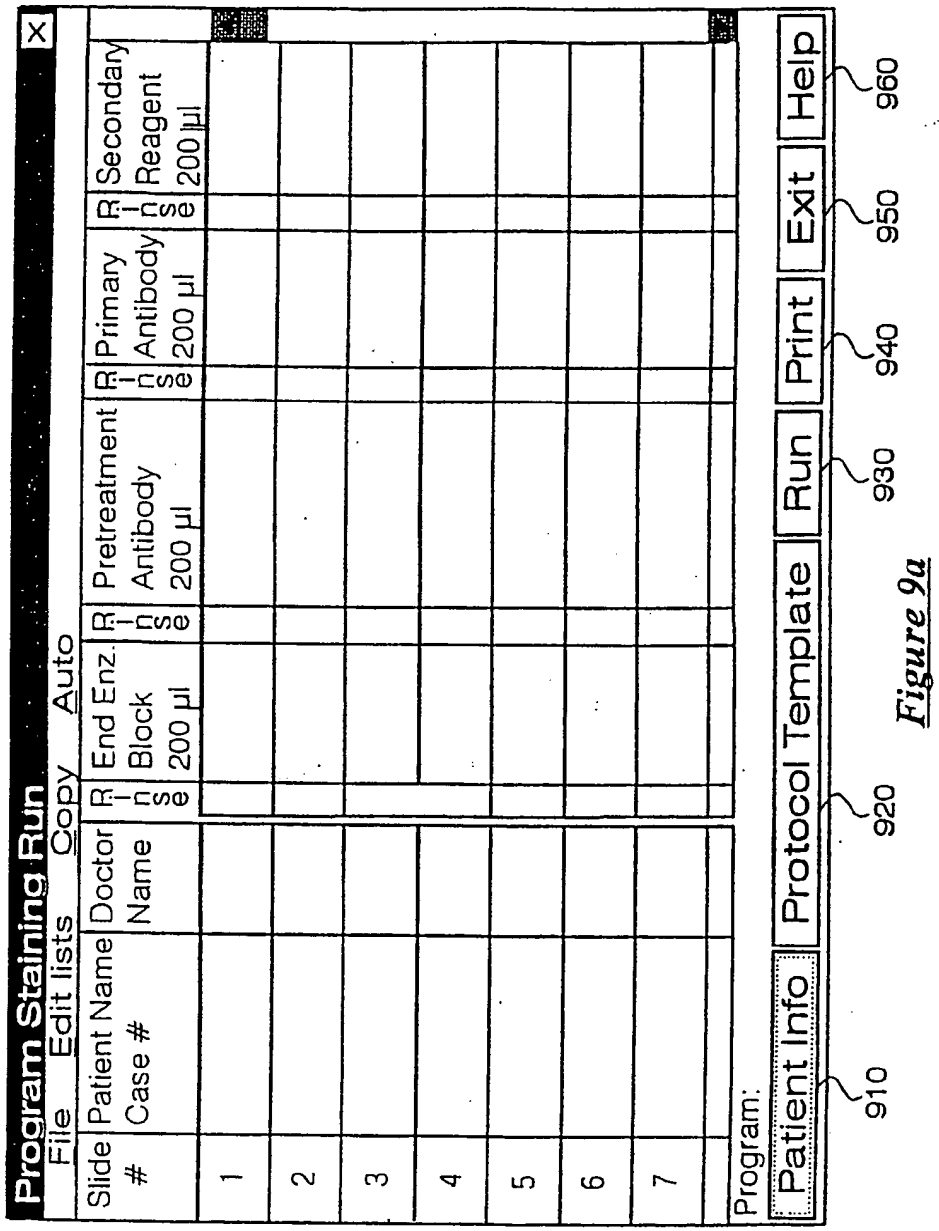
Program Staining Run
File Edit lists Copy Auto
Slide #
Patient Name Case #
Doctor Name
Rinse
End Enz. Block 200 µl
Rinse
Pretreatment Antibody 200 µl
Rinse
Primary Antibody 200 µl
Rinse
Secondary Reagent 200 µl
1
2
3
4
5
6
7
Program:
Patient Info
Protocol Template
Run
Print
Exit
Help
910
920
930
940
950
960

Figure 9a

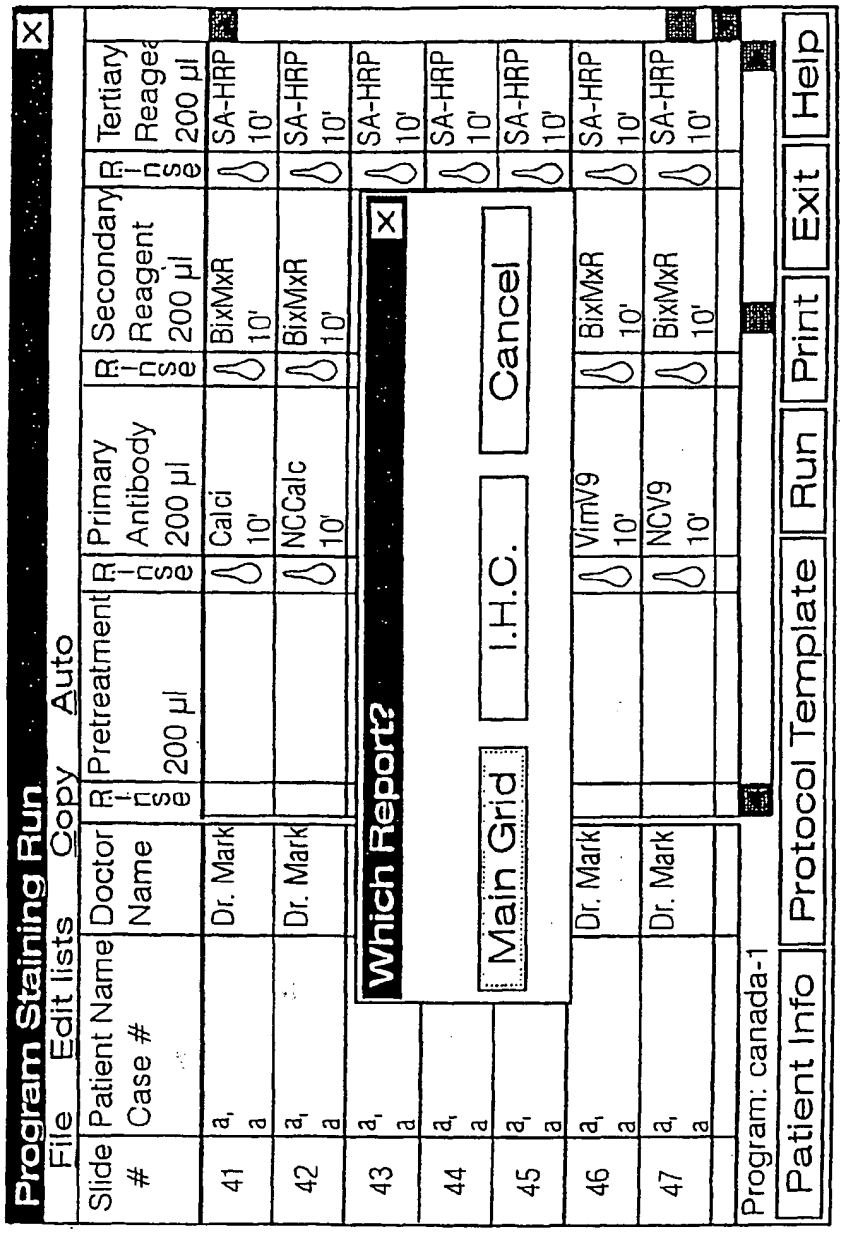
Program Staining Run
File Edit lists Copy Auto
Slide # Patient Name Case # Doctor Name Rinse Pretreatment 200 µl Rinse Primary Antibody 200 µl Rinse Secondary Reagent 200 µl Rinse Tertiary Reage 200 µl
41 a, a Dr. Mark Calci 10' BixMxR 10' SA-HRP 10'
42 a, a Dr. Mark NCCalc 10' BixMxR 10' SA-HRP 10'
43 a, a SA-HRP 10'
44 a, a SA-HRP 10'
45 a, a SA-HRP 10'
46 a, a Dr. Mark VimV9 10' BixMxR 10' SA-HRP 10'
47 a, a Dr. Mark NCV9 10' BixMxR 10' SA-HRP 10'
Which Report?
Main Grid
I.H.C.
Cancel
Program: canada-1
Patient Info
Protocol Template
Run
Print
Exit
Help

Figure 9b

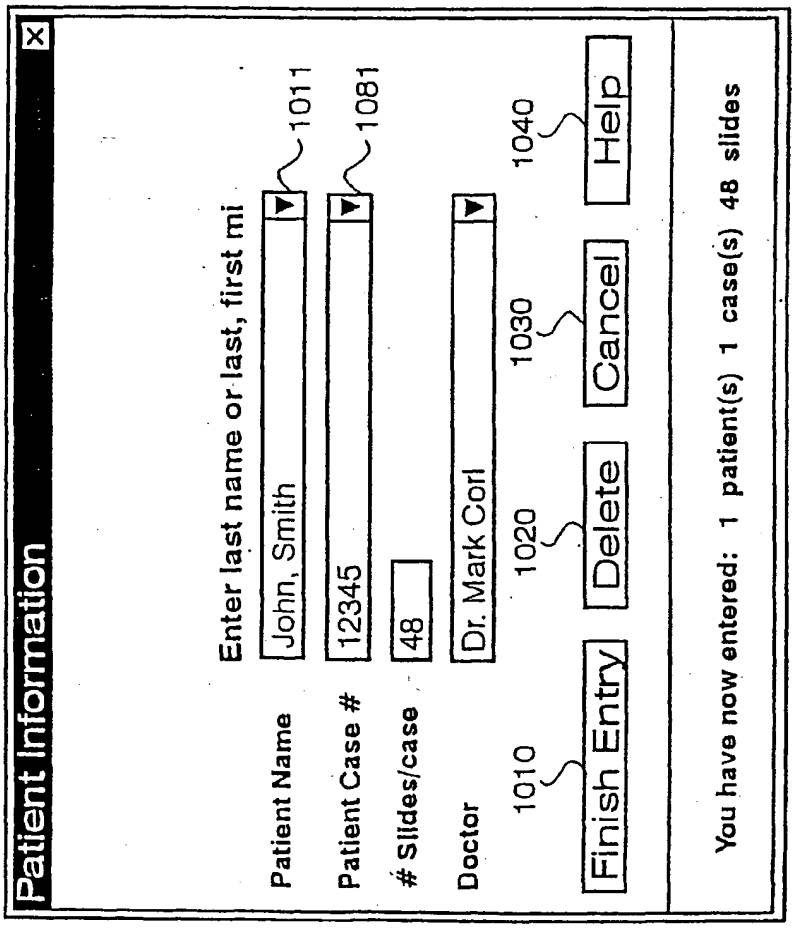
Patient Information
Enter last name or last, first mi
Patient Name
John, Smith
1011
Patient Case #
12345
1081
Slides/case
48
Doctor
Dr. Mark Corl
1010
1020
1030
1040
Finish Entry
Delete
Cancel
Help
You have now entered: 1 patient(s) 1 case(s) 48 slides

Figure 10

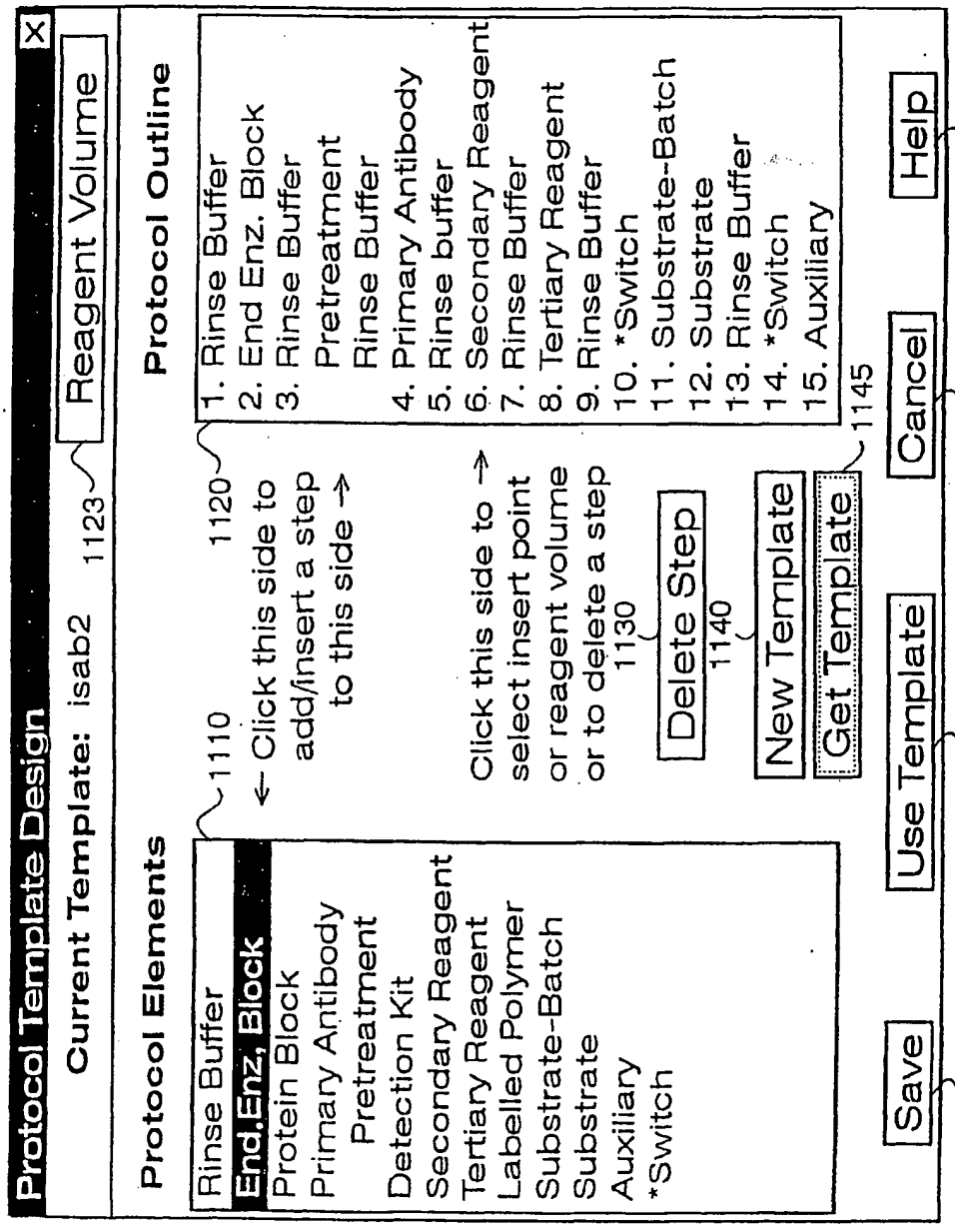
Protocol Template Design
Current Template: isab2
1123
Reagent Volume
Protocol Elements
Protocol Outline
1110
1120
Rinse Buffer
End.Enz. Block
Protein Block
Primary Antibody
Pretreatment
Detection Kit
Secondary Reagent
Tertiary Reagent
Labelled Polymer
Substrate-Batch
Substrate
Auxiliary
*Switch
← Click this side to add/insert a step
Click this side to → select insert point or reagent volume or to delete a step
1130
Delete Step
1140
New Template
Get Template
1145
1. Rinse Buffer
2. End Enz. Block
3. Rinse Buffer Pretreatment Rinse Buffer
4. Primary Antibody
5. Rinse buffer
6. Secondary Reagent
7. Rinse Buffer
8. Tertiary Reagent
9. Rinse Buffer
10. *Switch
11. Substrate-Batch
12. Substrate
13. Rinse Buffer
14. *Switch
15. Auxiliary
Save
1150
Use Template
1160
Cancel
1170
Help
1180

Figure 11

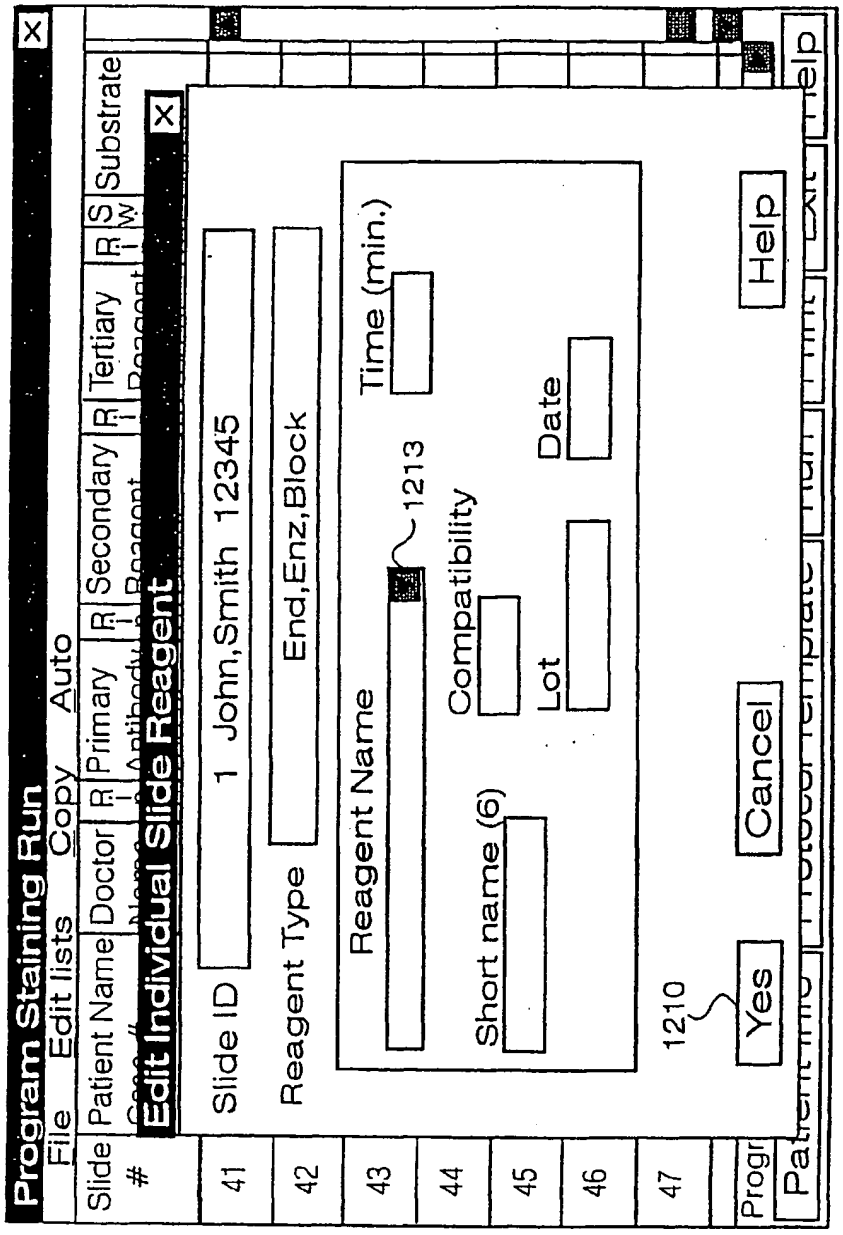
Program Staining Run
File Edit lists Copy Auto
Slide # Patient Name Doctor Primary Secondary Tertiary Substrate
Edit Individual Slide Reagent
Slide ID 1 John,Smith 12345
Reagent Type End,Enz,Block
Reagent Name
1213
Time (min.)
Compatibility
Short name (6)
Lot
Date
1210
Yes
Cancel
Help
41
42
43
44
45
46
47

Figure 12

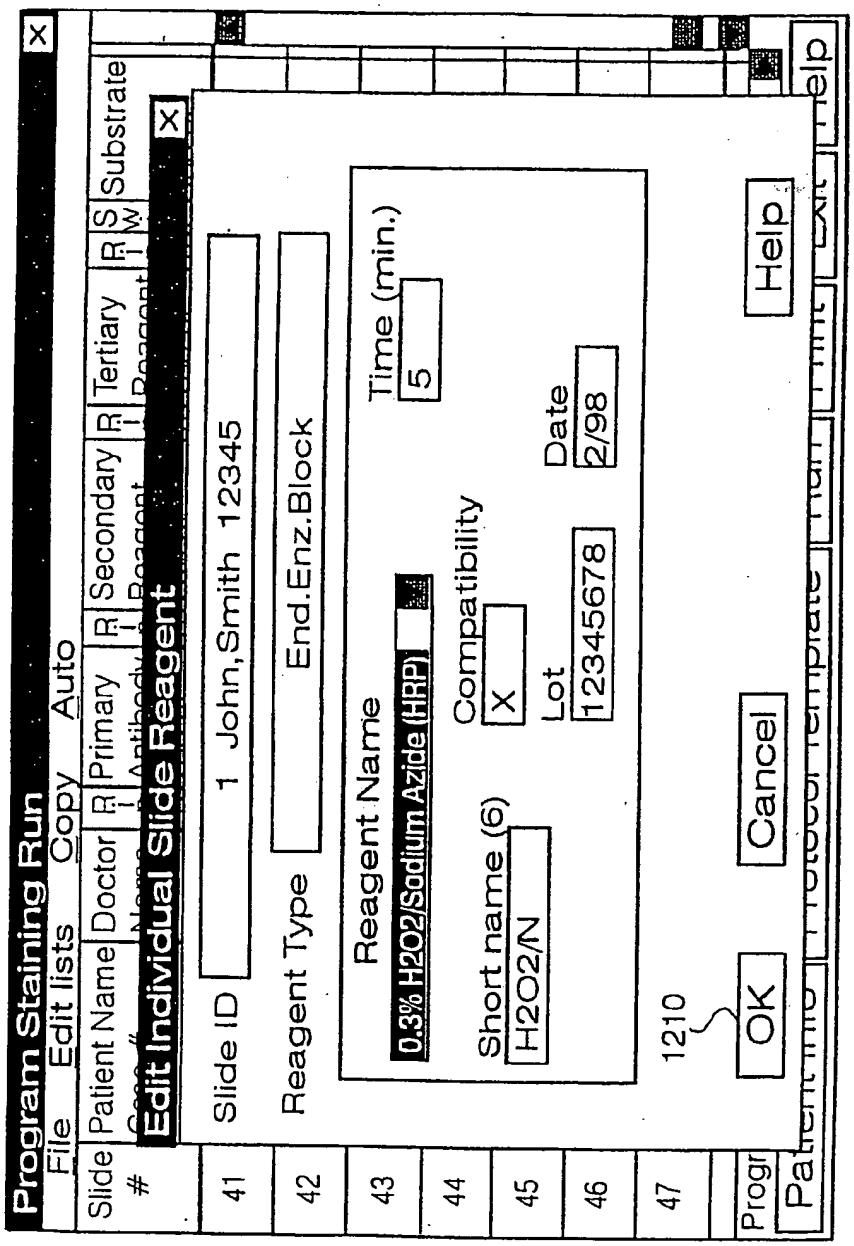
Program Staining Run
File Edit lists Copy Auto
Slide # Patient Name Doctor Primary Secondary Tertiary Substrate
Edit Individual Slide Reagent
Slide ID 1 John,Smith 12345
Reagent Type End.Enz.Block
Reagent Name
0.3% H2O2/Sodium Azide (HRP)
Time (min.) 5
Compatibility X
Short name (6) H2O2/N
Lot 12345678
Date 2/98
1210
OK
Cancel
Help
41
42
43
44
45
46
47

Figure 13

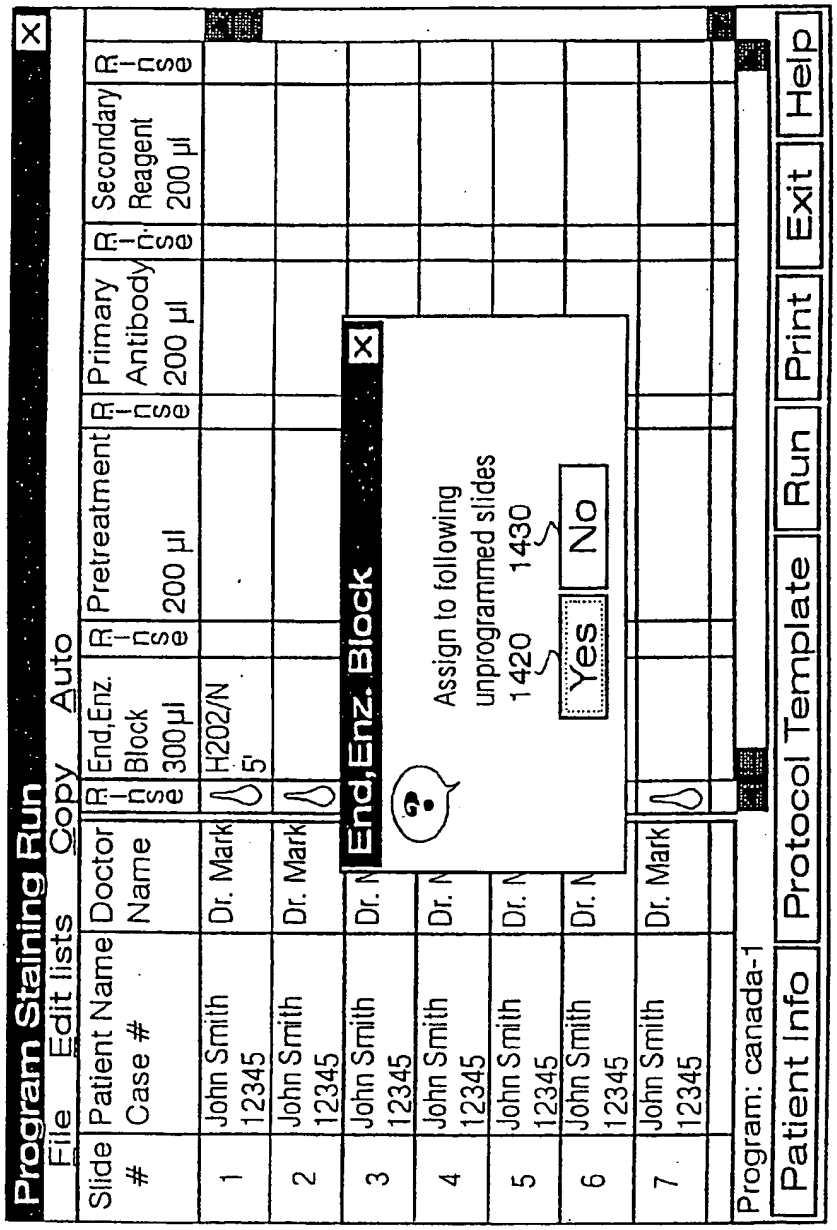
Program Staining Run
File Edit lists Copy Auto
Slide # | Patient Name Case # | Doctor Name | Rinse | End,Enz. Block 300µl | Rinse | Pretreatment 200 µl | Rinse | Primary Antibody 200 µl | Rinse | Secondary Reagent 200 µl | Rinse
1 | John Smith 12345 | Dr. Mark | | H202/N 5' | | | | | | | |
2 | John Smith 12345 | Dr. Mark | | | | | | | | | |
3 | John Smith 12345 | Dr. M | | | | | | | | | |
4 | John Smith 12345 | Dr. M | | | | | | | | | |
5 | John Smith 12345 | Dr. M | | | | | | | | | |
6 | John Smith 12345 | Dr. M | | | | | | | | | |
7 | John Smith 12345 | Dr. Mark | | | | | | | | | |
End,Enz. Block
Assign to following unprogrammed slides
1420 1430
Yes
No
Program: canada-1
Patient Info
Protocol Template
Run
Print
Exit
Help

Figure 14

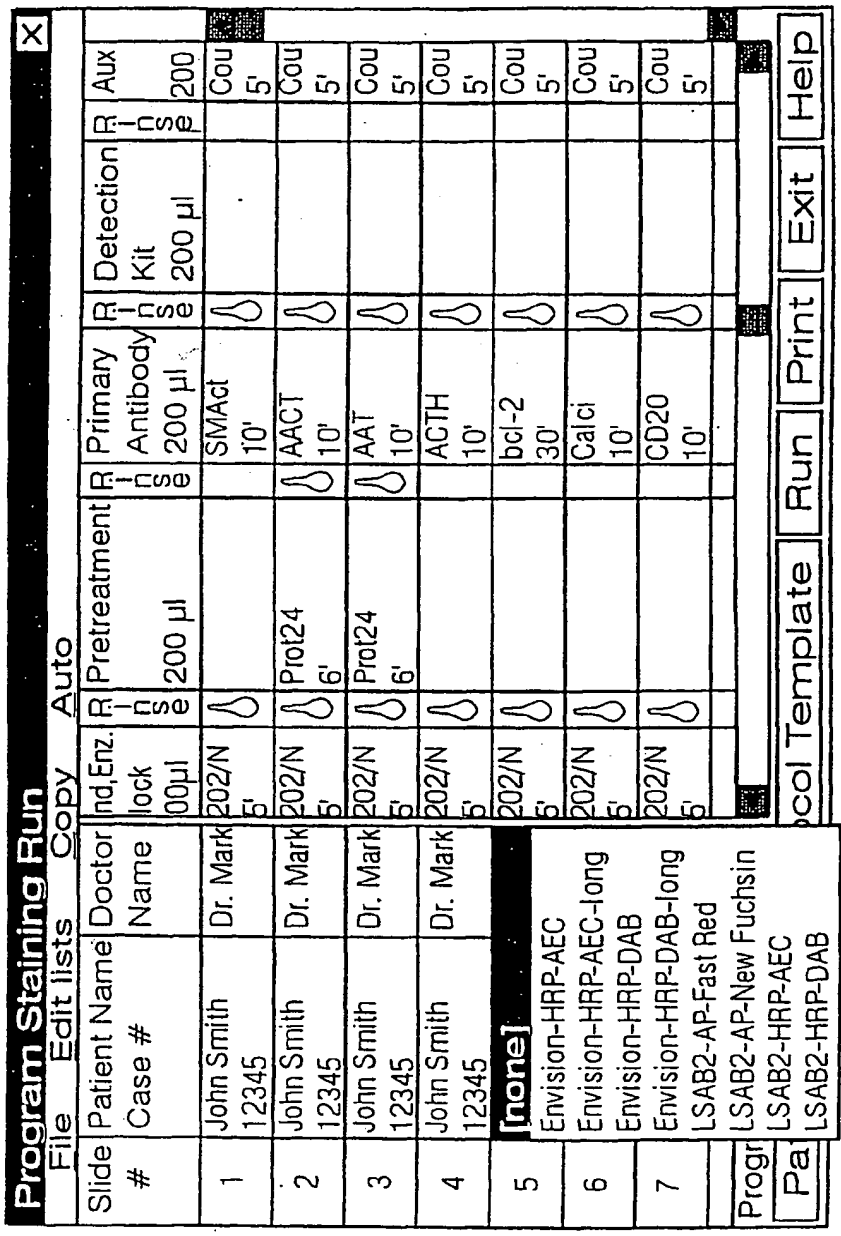
Program Staining Run
File Edit lists Copy Auto
Slide # | Patient Name Case # | Doctor Name | nd,Enz. lock 00µl | Rinse | Pretreatment 200 µl | Rinse | Primary Antibody 200 µl | Rinse | Detection Kit 200 µl | Rinse | Aux 200
1 | John Smith 12345 | Dr. Mark | 202/N 5' | | SMAct 10' | | | Cou 5'
2 | John Smith 12345 | Dr. Mark | 202/N 5' | Prot24 6' | AACT 10' | | | Cou 5'
3 | John Smith 12345 | Dr. Mark | 202/N 5' | Prot24 6' | AAT 10' | | | Cou 5'
4 | John Smith 12345 | Dr. Mark | 202/N 5' | | ACTH 10' | | | Cou 5'
5 | [none] | | 202/N 5' | | bcl-2 30' | | | Cou 5'
6 | Envision-HRP-AEC Envision-HRP-AEC-long Envision-HRP-DAB | | 202/N 5' | | Calci 10' | | | Cou 5'
7 | Envision-HRP-DAB-long LSAB2-AP-Fast Red LSAB2-AP-New Fuchsin | | 202/N 5' | | CD20 10' | | | Cou 5'
Progr
Pa
LSAB2-HRP-AEC
LSAB2-HRP-DAB
pcol Template
Run
Print
Exit
Help
1510

Figure 15

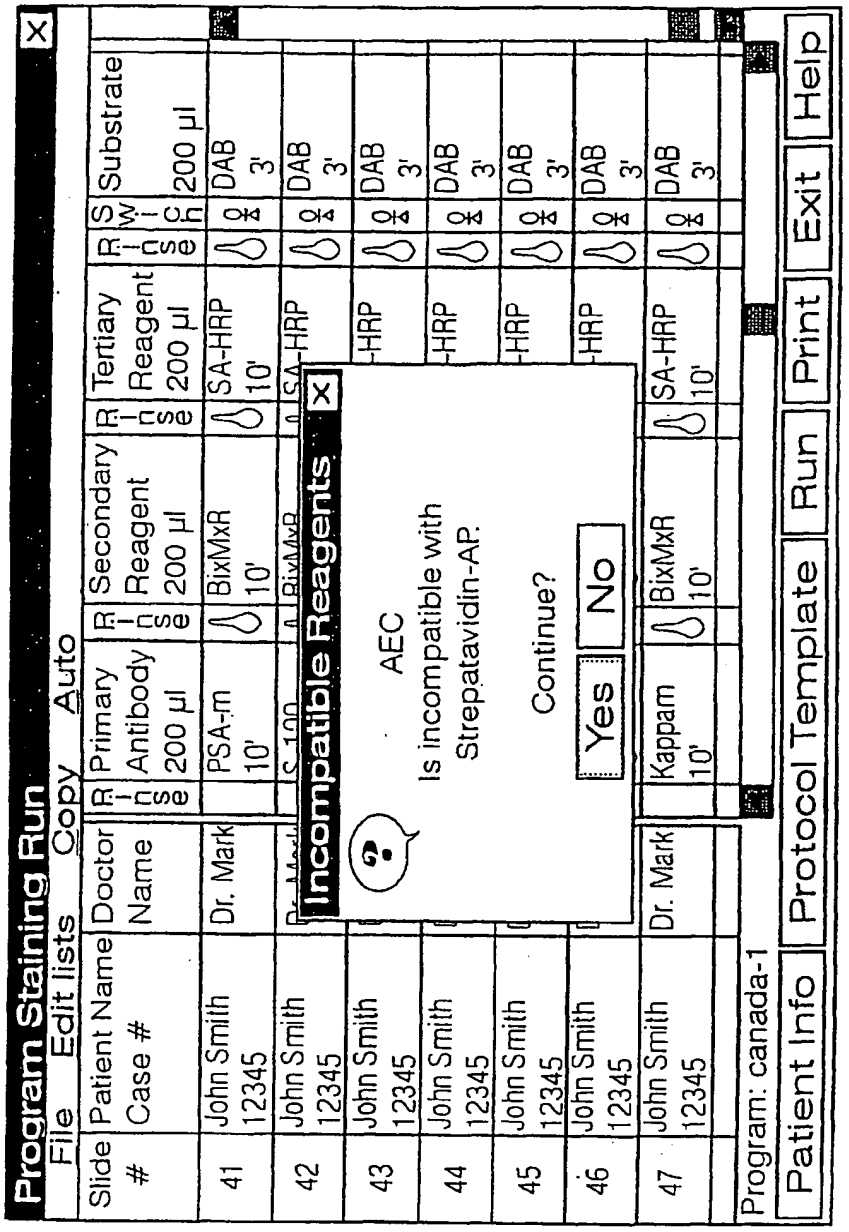
Program Staining Run
File Edit lists Copy Auto
Slide # | Patient Name Case # | Doctor Name | Rinse | Primary Antibody 200 µl | Rinse | Secondary Reagent 200 µl | Rinse | Tertiary Reagent 200 µl | Rinse | Switch | Substrate 200 µl
41 | John Smith 12345 | Dr. Mark | PSA-m 10' | BixMxR 10' | SA-HRP 10' | DAB 3'
42 | John Smith 12345 | SA-HRP | DAB 3'
43 | John Smith 12345 | -HRP | DAB 3'
44 | John Smith 12345 | -HRP | DAB 3'
45 | John Smith 12345 | -HRP | DAB 3'
46 | John Smith 12345 | -HRP | DAB 3'
47 | John Smith 12345 | Dr. Mark | Kappam 10' | BixMxR 10' | SA-HRP 10' | DAB 3'
Incompatible Reagents
AEC
Is incompatible with
Strepatavidin-AP.
Continue?
Yes
No
Program: canada-1
Patient Info
Protocol Template
Run
Print
Exit
Help

Figure 16

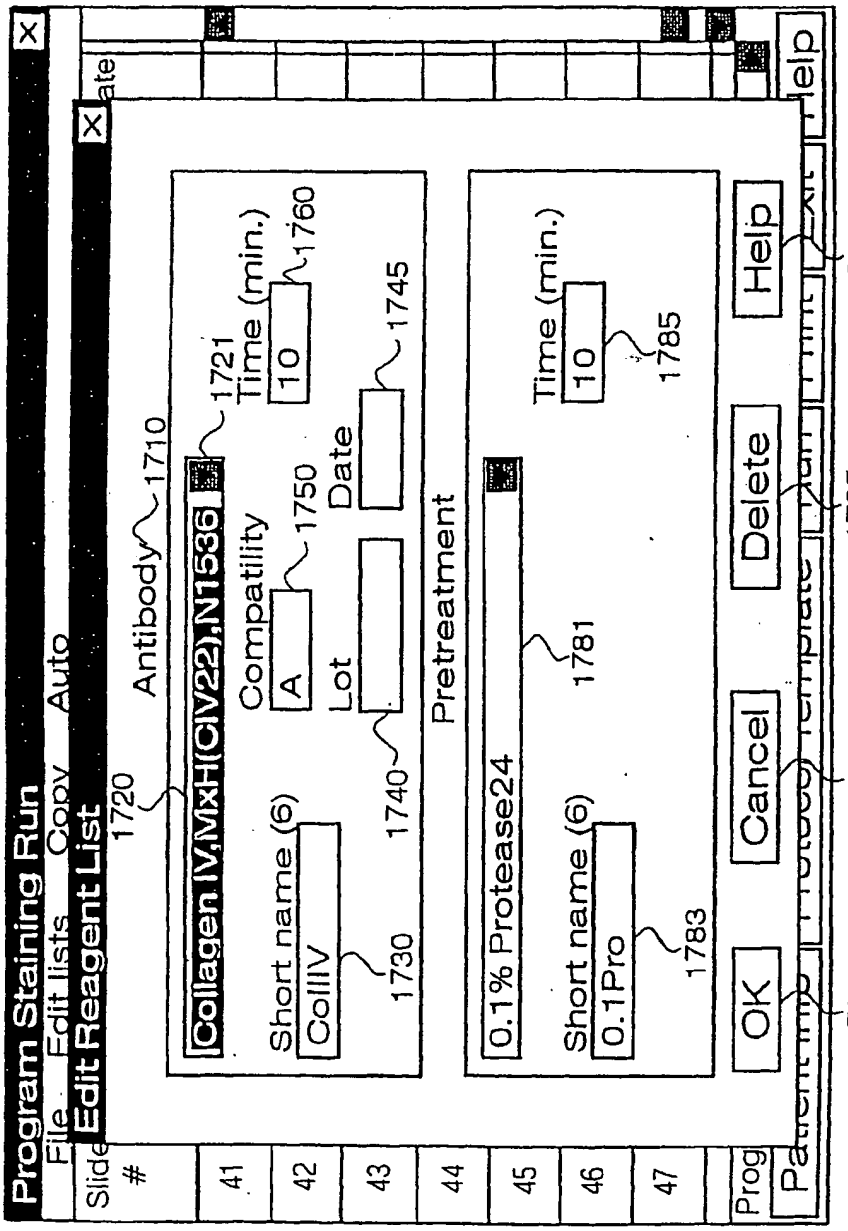
Program Staining Run
File Edit lists Copy Auto
Edit Reagent List
Slide #
41
42
43
44
45
46
47
Prog
Antibody
1710
1720
Collagen IV,MxHCIV22,N1536
1721
Short name (6)
CollIV
1730
Compatility
A
1750
Lot
1740
Time (min.)
10
1760
Date
1745
Pretreatment
0.1% Protease24
1781
Short name (6)
0.1Pro
1783
Time (min.)
10
1785
OK
Cancel
Delete
Help
1791
1793
1795
1797

Figure 17

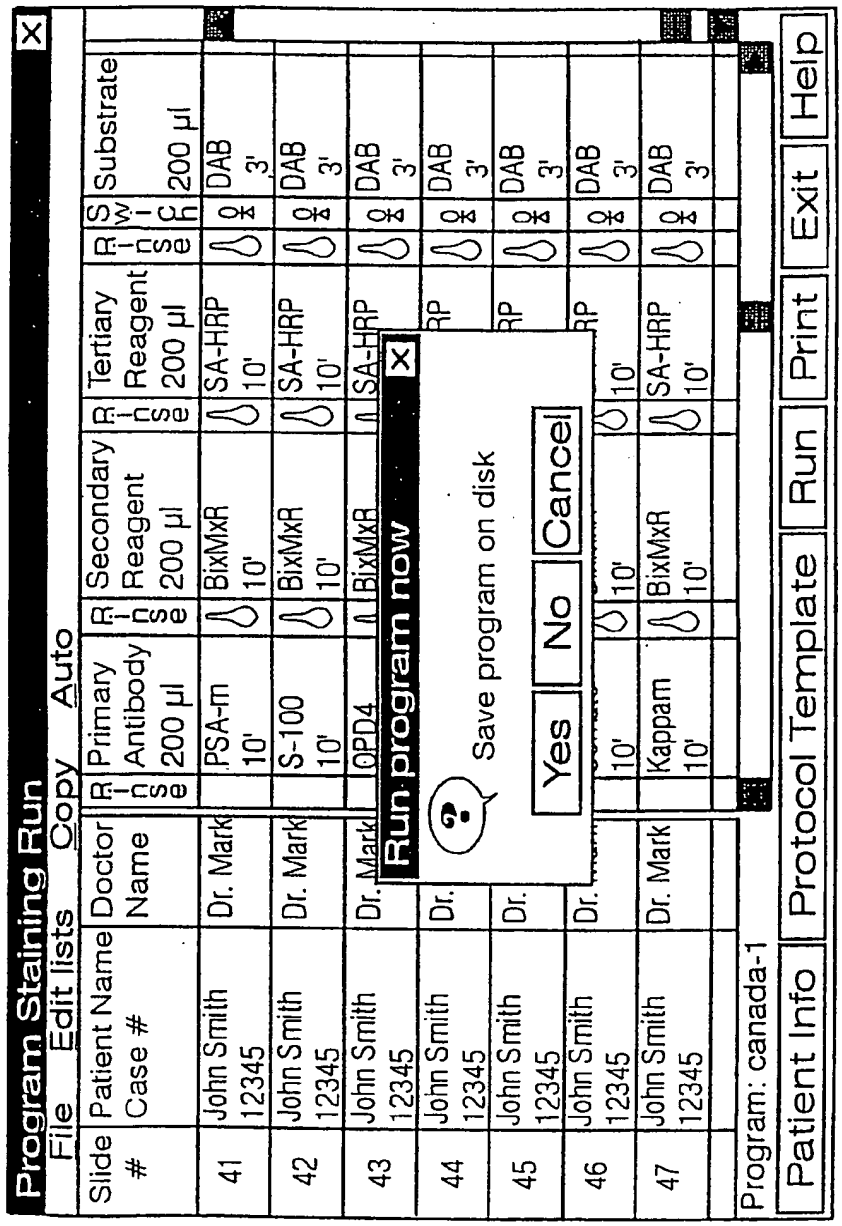
Program Staining Run
File Edit lists Copy Auto
Slide # | Patient Name Case # | Doctor Name | Rinse | Primary Antibody 200 µl | Rinse | Secondary Reagent 200 µl | Rinse | Tertiary Reagent 200 µl | Rinse | Substrate 200 µl
41 | John Smith 12345 | Dr. Mark | PSA-m 10' | BixMxR 10' | SA-HRP 10' | DAB 3'
42 | John Smith 12345 | Dr. Mark | S-100 10' | BixMxR 10' | SA-HRP 10' | DAB 3'
43 | John Smith 12345 | Dr. Mark | OPD4 | BixMxR | SA-HRP | DAB 3'
44 | John Smith 12345 | Dr. | 10' | 10' | DAB 3'
45 | John Smith 12345 | Dr. | DAB 3'
46 | John Smith 12345 | Dr. | 10' | 10' | DAB 3'
47 | John Smith 12345 | Dr. Mark | Kappam 10' | BixMxR 10' | SA-HRP 10' | DAB 3'
Run program now
Save program on disk
Yes
No
Cancel
Program: canada-1
Patient Info
Protocol Template
Run
Print
Exit
Help

Figure 18

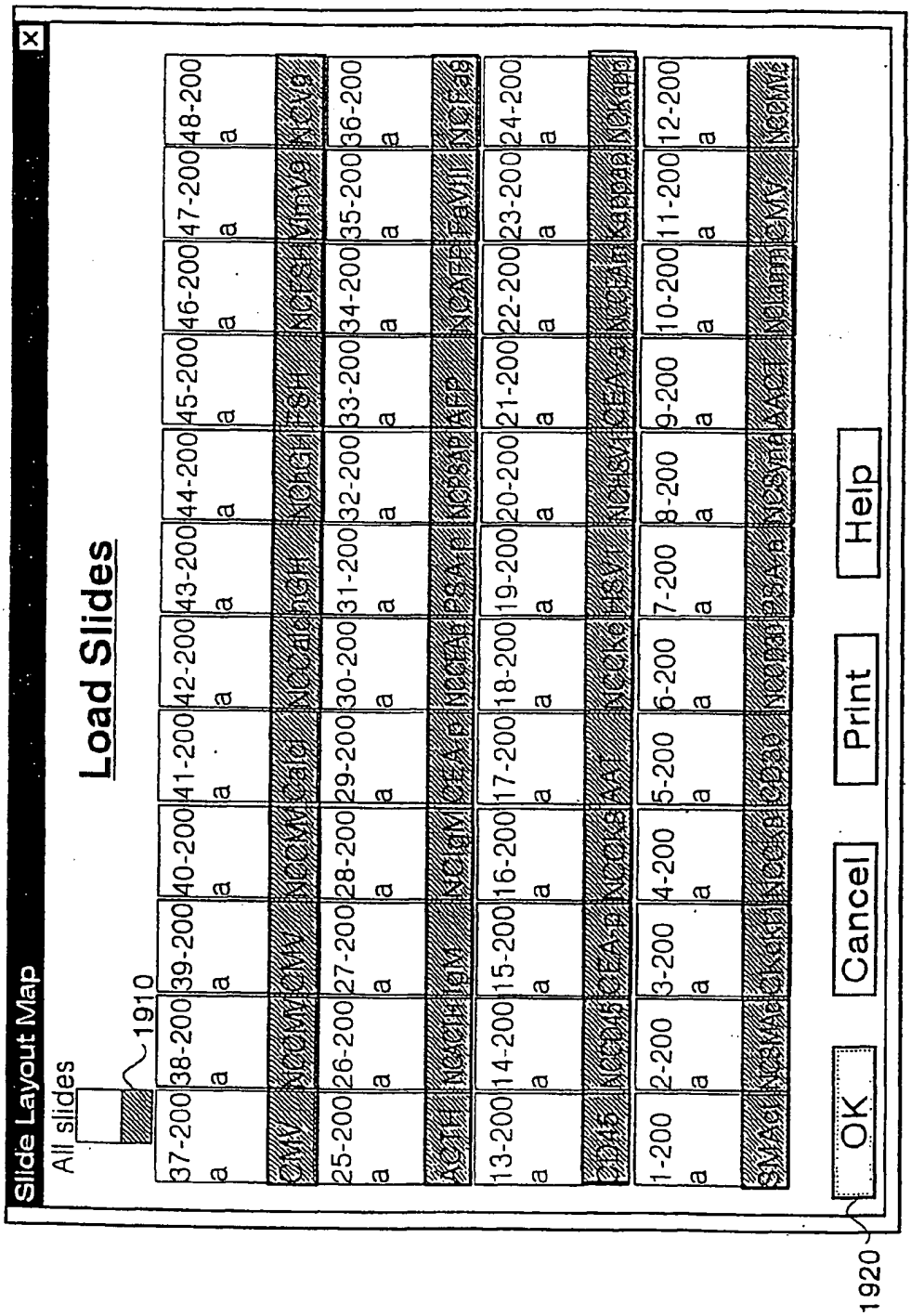
Slide Layout Map
All slides
Load Slides
1910
1920
OK
Cancel
Print
Help

Figure 19

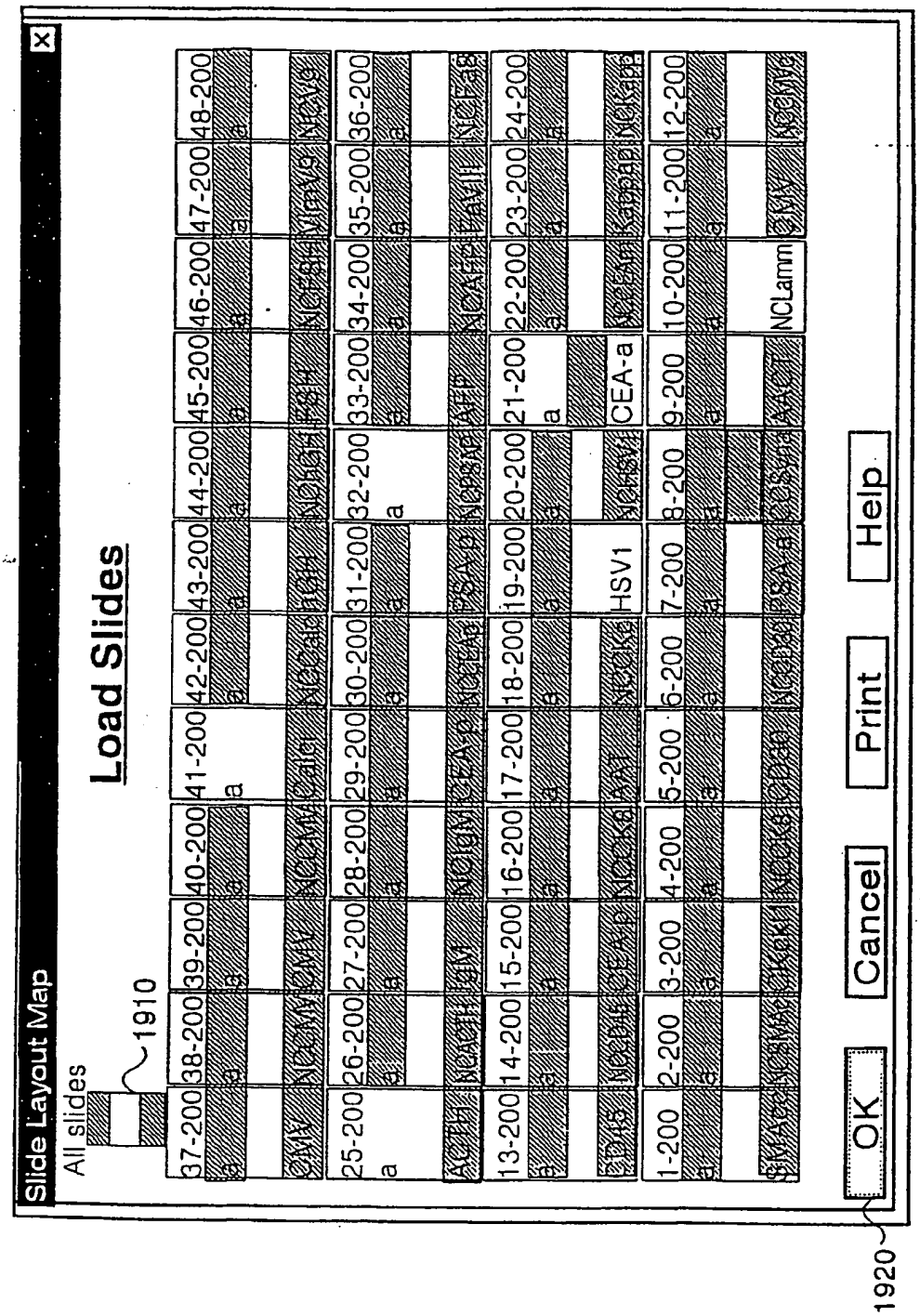
Slide Layout Map
All slides
Load Slides
1910
1920
OK
Cancel
Print
Help

Figure 20

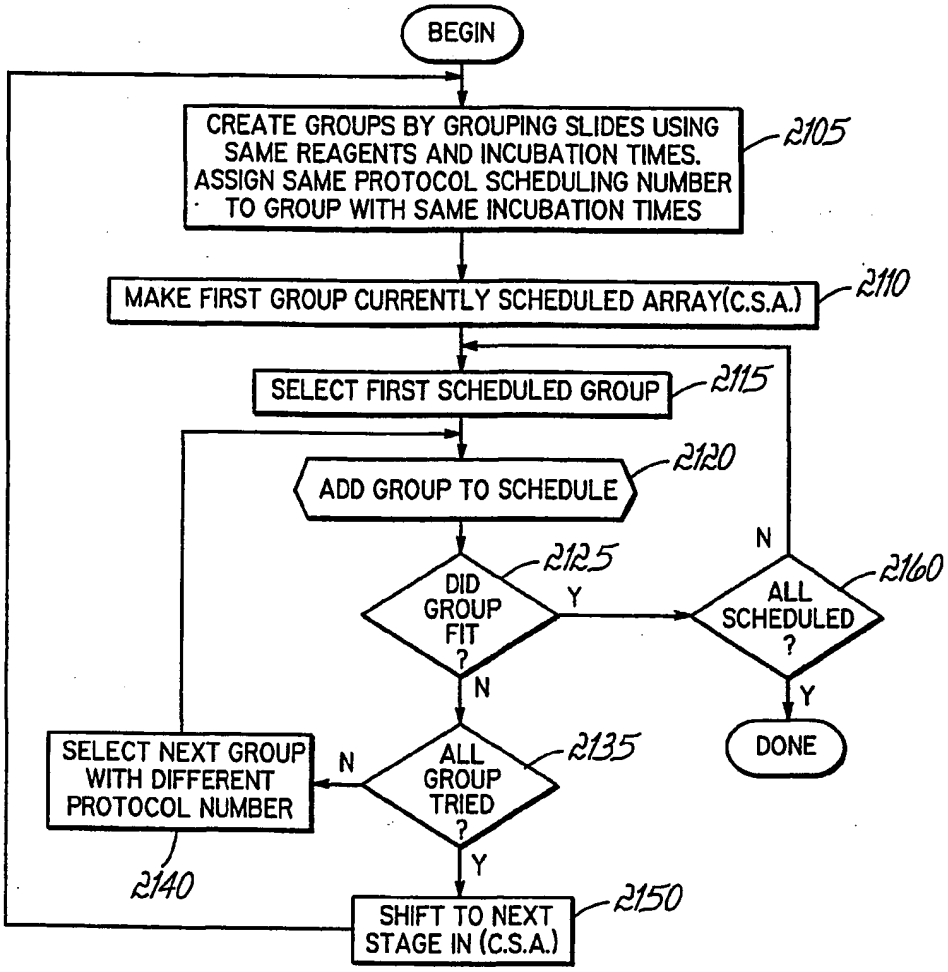
BEGIN
CREATE GROUPS BY GROUPING SLIDES USING SAME REAGENTS AND INCUBATION TIMES. ASSIGN SAME PROTOCOL SCHEDULING NUMBER TO GROUP WITH SAME INCUBATION TIMES
2105
MAKE FIRST GROUP CURRENTLY SCHEDULED ARRAY(C.S.A.)
2110
SELECT FIRST SCHEDULED GROUP
2115
ADD GROUP TO SCHEDULE
2120
DID GROUP FIT ?
2125
Y
N
ALL SCHEDULED ?
2160
N
Y
DONE
ALL GROUP TRIED ?
2135
N
Y
SELECT NEXT GROUP WITH DIFFERENT PROTOCOL NUMBER
2140
SHIFT TO NEXT STAGE IN (C.S.A.)
2150

FIG. 21

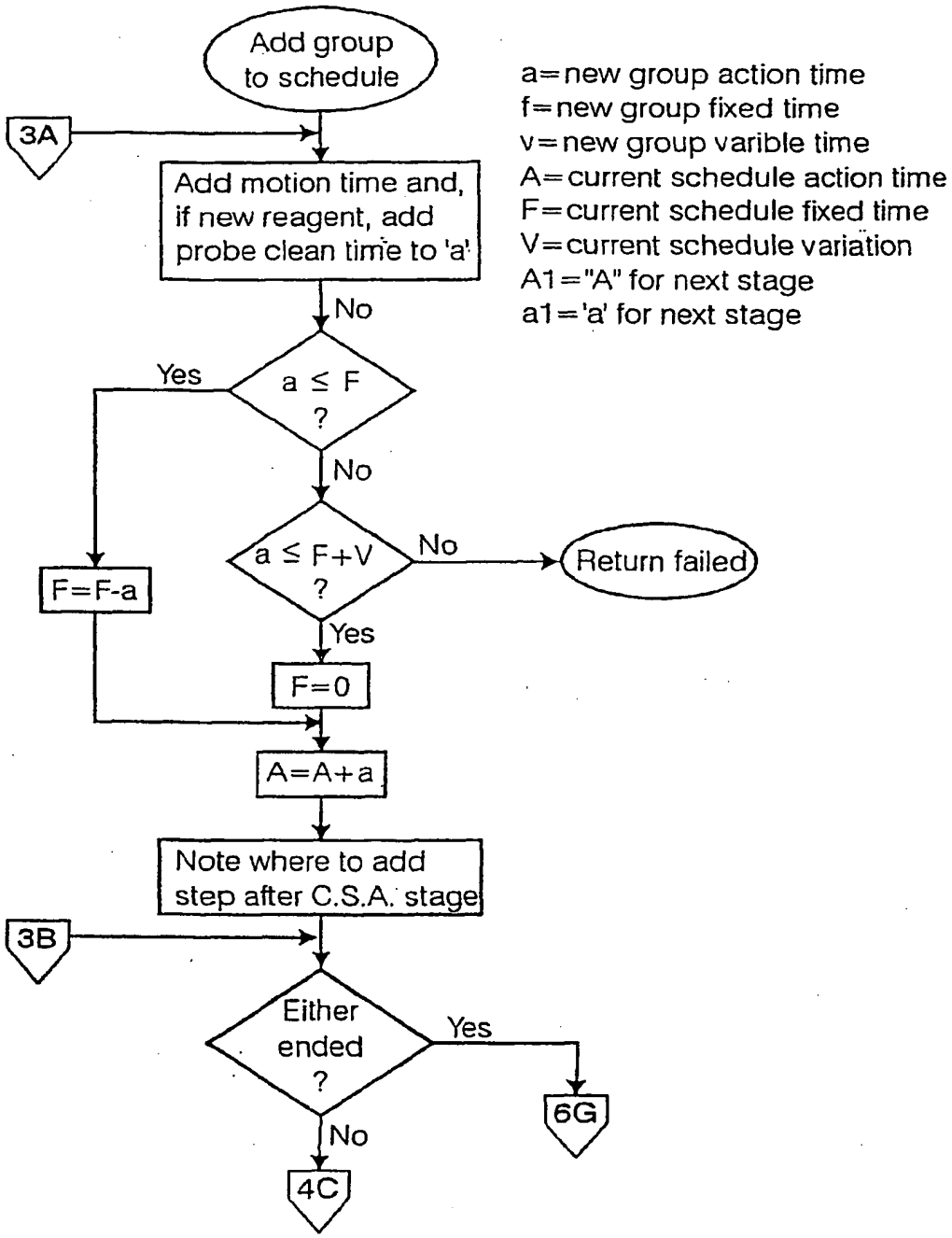
Add group to schedule
3A
Add motion time and, if new reagent, add probe clean time to 'a'
No
Yes
a ≤ F ?
No
a ≤ F+V ?
No
Return failed
F=F-a
Yes
F=0
A=A+a
Note where to add step after C.S.A. stage
3B
Either ended ?
Yes
6G
No
4C
a=new group action time
f=new group fixed time
v=new group varible time
A=current schedule action time
F=current schedule fixed time
V=current schedule variation
A1="A" for next stage
a1='a' for next stage

Figure 22a

Add New Group (cont.)

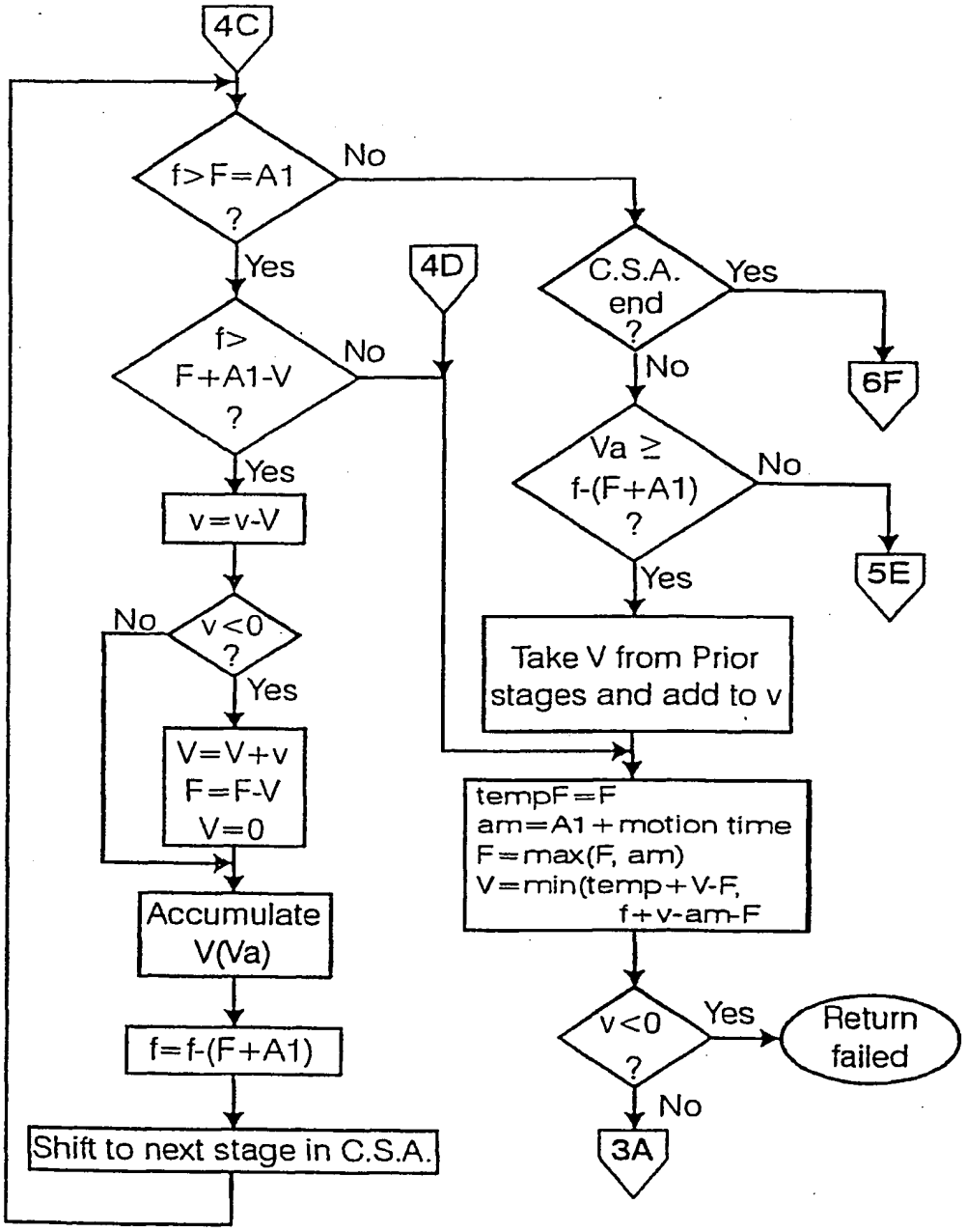

Figure 22b

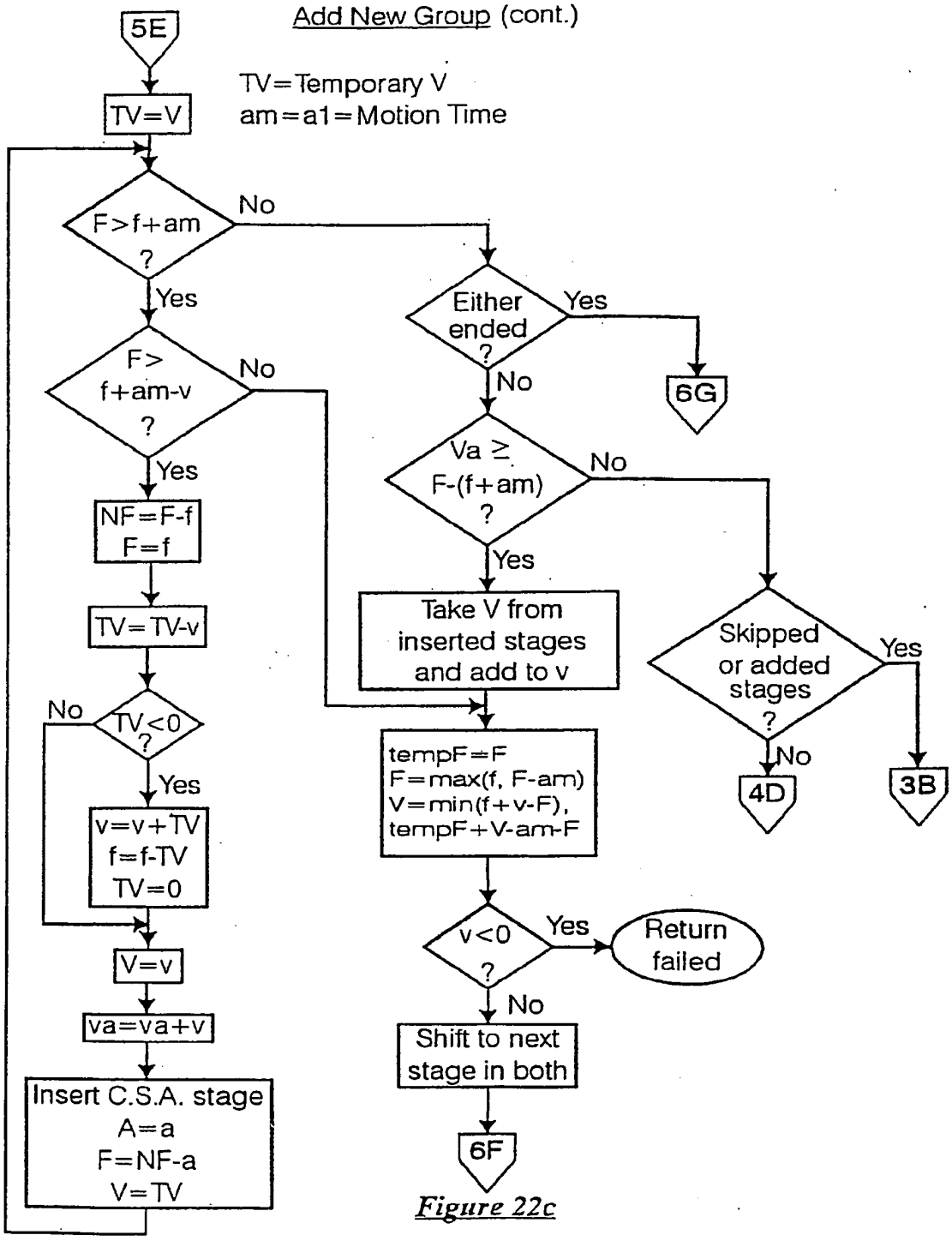
Add New Group (cont.)
5E
TV=Temporary V
am=a1=Motion Time
TV=V
F>f+am ?
No
Yes
F> f+am-v ?
No
Yes
NF=F-f
F=f
TV=TV-v
No
TV<0 ?
Yes
v=v+TV
f=f-TV
TV=0
V=v
va=va+v
Insert C.S.A. stage
A=a
F=NF-a
V=TV
Either ended ?
Yes
6G
No
Va ≥ F-(f+am) ?
No
Yes
Take V from inserted stages and add to v
Skipped or added stages ?
Yes
No
4D
3B
tempF=F
F=max(f, F-am)
V=min(f+v-F), tempF+V-am-F
v<0 ?
Yes
Return failed
No
Shift to next stage in both
6F

Figure 22c

Add New Group (cont.)

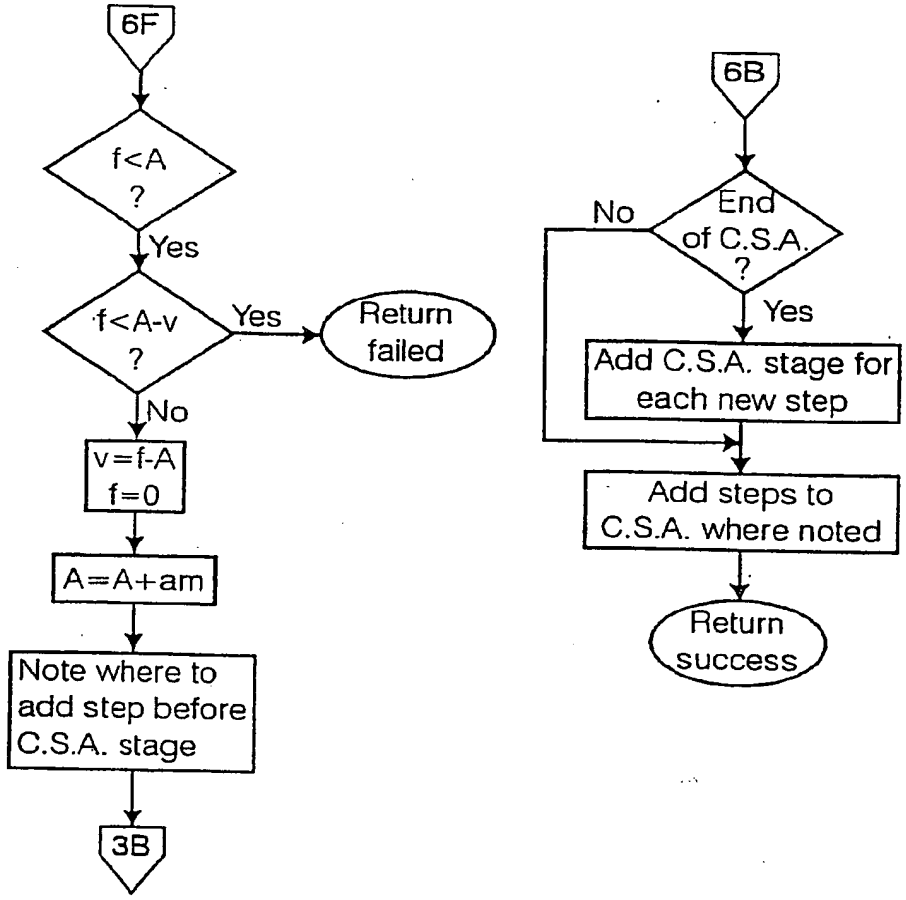

Figure 22d

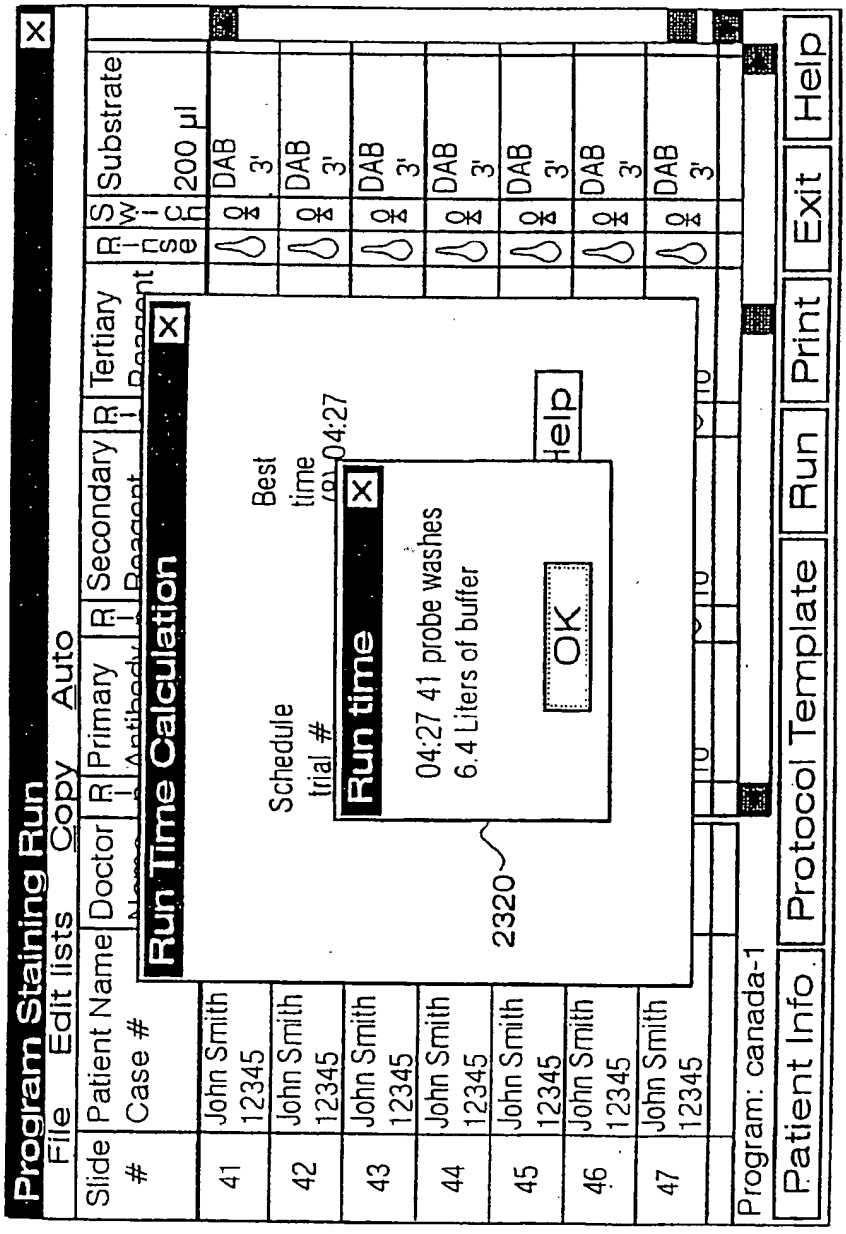
Program Staining Run
File Edit lists Copy Auto
Slide # Patient Name Case # Doctor Primary Secondary Tertiary Reagent Sequence Substrate 200 µl
41 John Smith 12345 DAB 3'
42 John Smith 12345 DAB 3'
43 John Smith 12345 DAB 3'
44 John Smith 12345 DAB 3'
45 John Smith 12345 DAB 3'
46 John Smith 12345 DAB 3'
47 John Smith 12345 DAB 3'
Run Time Calculation
Schedule trial #
Best time
04:27
Run time
04:27 41 probe washes
6.4 Liters of buffer
OK
Help
2320
Program: canada-1
Patient Info
Protocol Template
Run
Print
Exit
Help

Figure 23

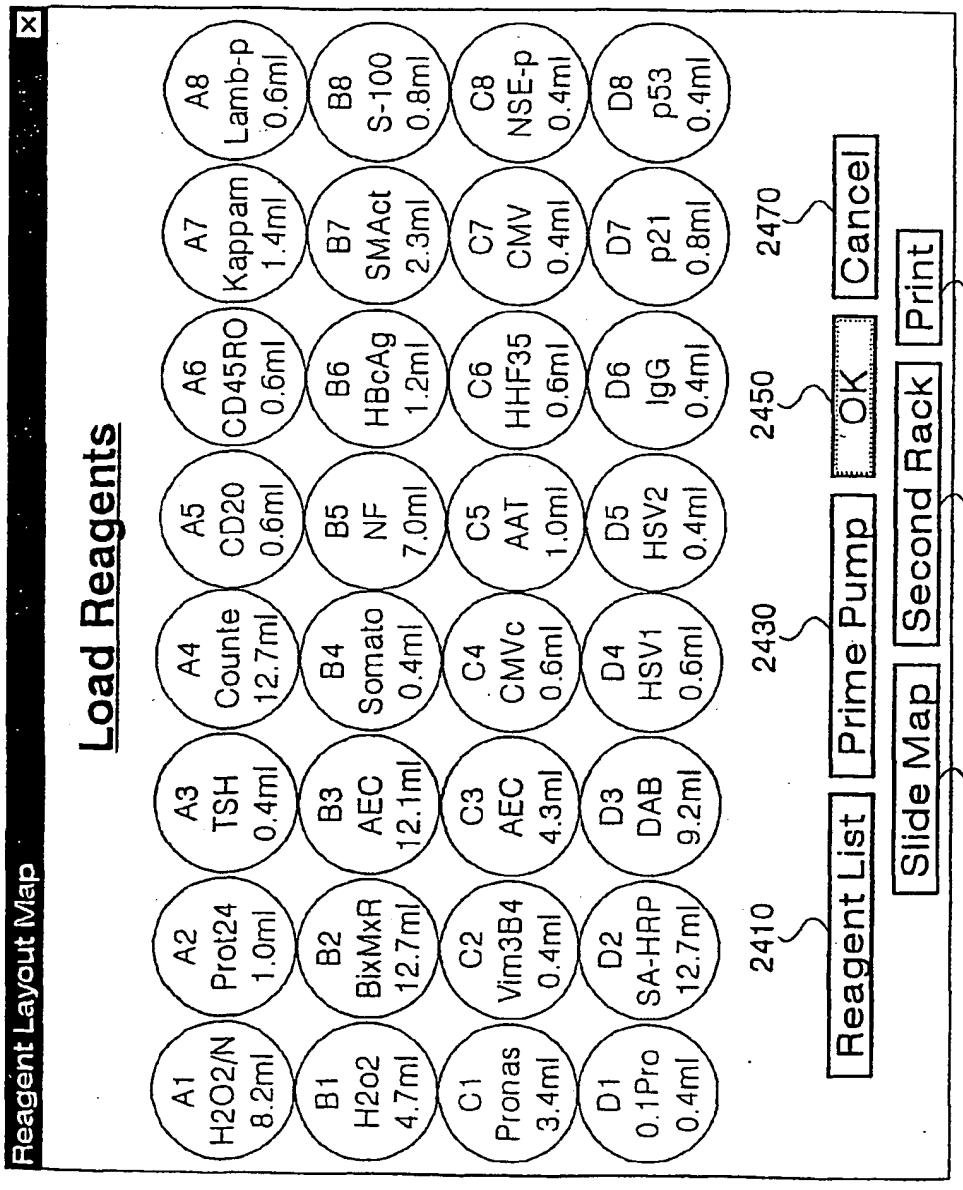
Reagent Layout Map
Load Reagents
A1 H2O2/N 8.2ml
A2 Prot24 1.0ml
A3 TSH 0.4ml
A4 Counte 12.7ml
A5 CD20 0.6ml
A6 CD45RO 0.6ml
A7 Kappam 1.4ml
A8 Lamb-p 0.6ml
B1 H2o2 4.7ml
B2 BixMxR 12.7ml
B3 AEC 12.1ml
B4 Somato 0.4ml
B5 NF 7.0ml
B6 HBcAg 1.2ml
B7 SMAct 2.3ml
B8 S-100 0.8ml
C1 Pronas 3.4ml
C2 Vim3B4 0.4ml
C3 AEC 4.3ml
C4 CMVc 0.6ml
C5 AAT 1.0ml
C6 HHF35 0.6ml
C7 CMV 0.4ml
C8 NSE-p 0.4ml
D1 0.1Pro 0.4ml
D2 SA-HRP 12.7ml
D3 DAB 9.2ml
D4 HSV1 0.6ml
D5 HSV2 0.4ml
D6 IgG 0.4ml
D7 p21 0.8ml
D8 p53 0.4ml
Reagent List
Prime Pump
OK
Cancel
Slide Map
Second Rack
Print
2410
2420
2430
2440
2450
2460
2470

Figure 24

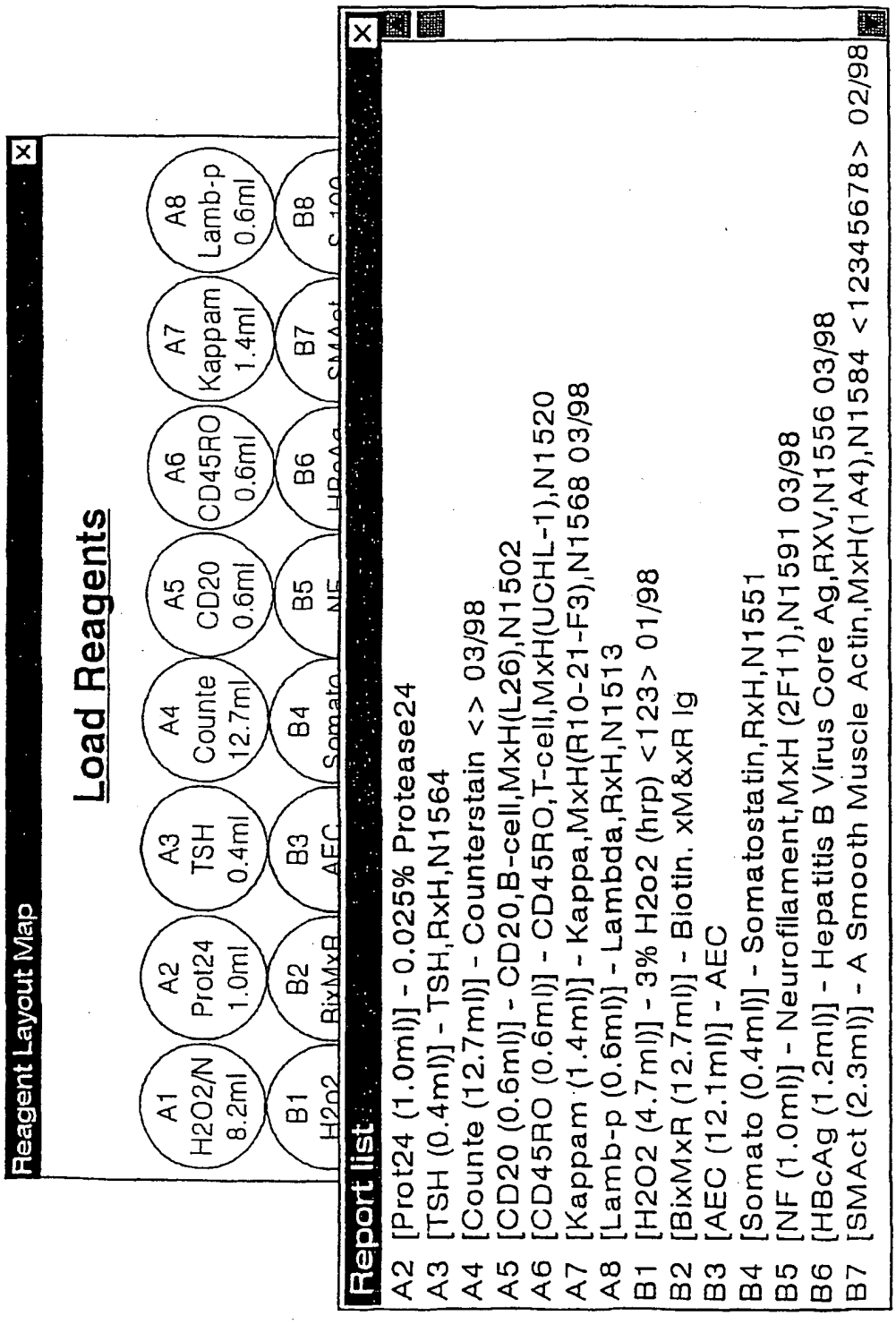
Reagent Layout Map
Load Reagents
A1 H2O2/N 8.2ml
A2 Prot24 1.0ml
A3 TSH 0.4ml
A4 Counte 12.7ml
A5 CD20 0.6ml
A6 CD45RO 0.6ml
A7 Kappam 1.4ml
A8 Lamb-p 0.6ml
B1 H2o2
B2 BixMxR
B3 AEC
B4 Somato
B5 NF
B6
B7 SMAct
B8
Report list
A2 [Prot24 (1.0ml)] - 0.025% Protease24
A3 [TSH (0.4ml)] - TSH,RxH,N1564
A4 [Counte (12.7ml)] - Counterstain <> 03/98
A5 [CD20 (0.6ml)] - CD20,B-cell,MxH(L26),N1502
A6 [CD45RO (0.6ml)] - CD45RO,T-cell,MxH(UCHL-1),N1520
A7 [Kappam (1.4ml)] - Kappa,MxH(R10-21-F3),N1568 03/98
A8 [Lamb-p (0.6ml)] - Lambda,RxH,N1513
B1 [H2O2 (4.7ml)] - 3% H2o2 (hrp) <123> 01/98
B2 [BixMxR (12.7ml)] - Biotin, xM&xR Ig
B3 [AEC (12.1ml)] - AEC
B4 [Somato (0.4ml)] - Somatostatin,RxH,N1551
B5 [NF (1.0ml)] - Neurofilament,MxH (2F11),N1591 03/98
B6 [HBcAg (1.2ml)] - Hepatitis B Virus Core Ag,RXV,N1556 03/98
B7 [SMAct (2.3ml)] - A Smooth Muscle Actin,MxH(1A4),N1584 <12345678> 02/98

Figure 25

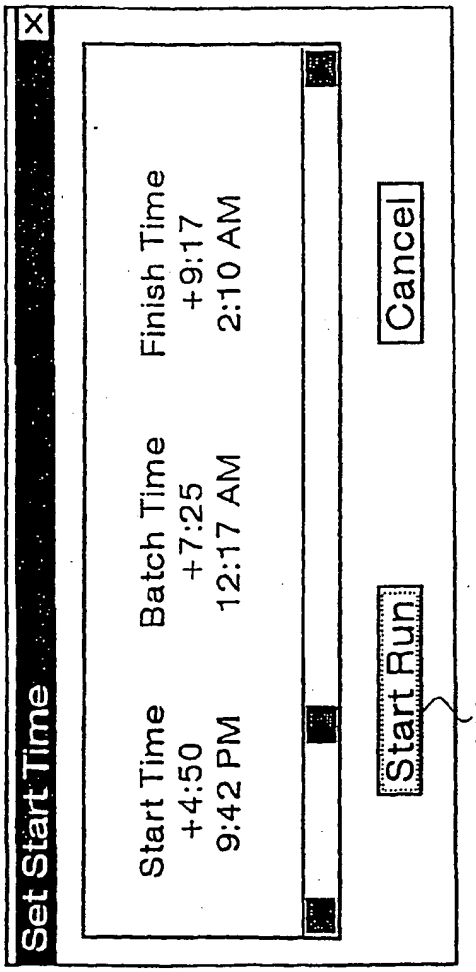
Set Start Time
Start Time
+4:50
9:42 PM
Batch Time
+7:25
12:17 AM
Finish Time
+9:17
2:10 AM
Start Run
Cancel
2160

Figure 26

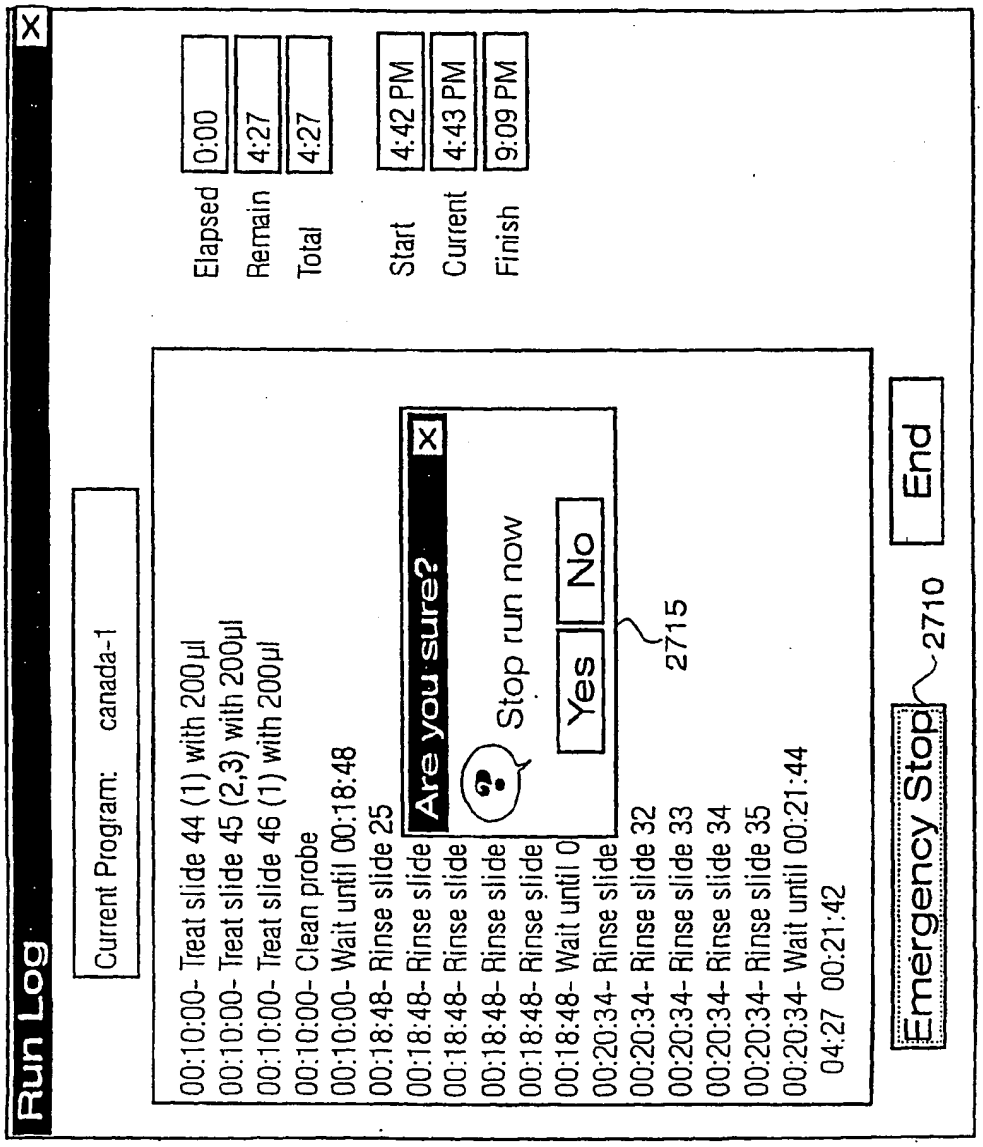
Run Log
Current Program: canada-1
00:10:00- Treat slide 44 (1) with 200µl
00:10:00- Treat slide 45 (2,3) with 200µl
00:10:00- Treat slide 46 (1) with 200µl
00:10:00- Clean probe
00:10:00- Wait until 00:18:48
00:18:48- Rinse slide 25
00:18:48- Rinse slide
00:18:48- Rinse slide
00:18:48- Rinse slide
00:18:48- Rinse slide
00:18:48- Wait until 0
00:20:34- Rinse slide
00:20:34- Rinse slide 32
00:20:34- Rinse slide 33
00:20:34- Rinse slide 34
00:20:34- Rinse slide 35
00:20:34- Wait until 00:21:44
04:27 00:21:42
Are you sure?
Stop run now
Yes
No
2715
Emergency Stop
2710
End
Elapsed 0:00
Remain 4:27
Total 4:27
Start 4:42 PM
Current 4:43 PM
Finish 9:09 PM

Figure 27

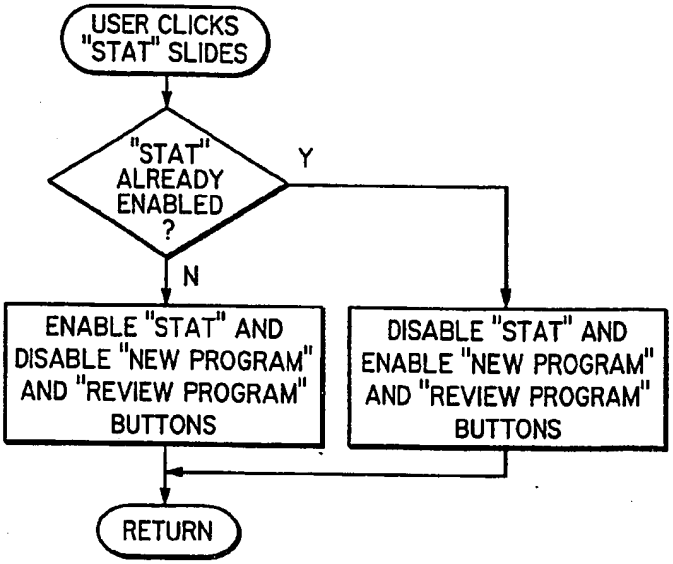

FIG. 29

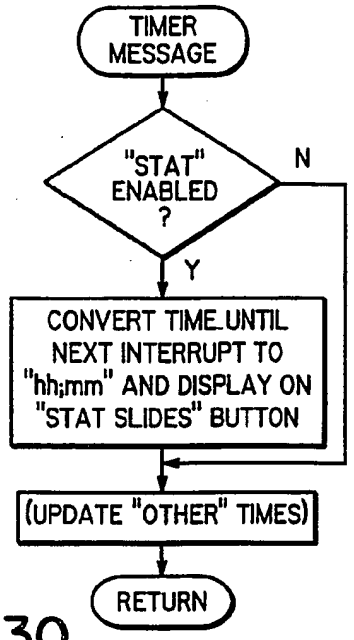

FIG. 30

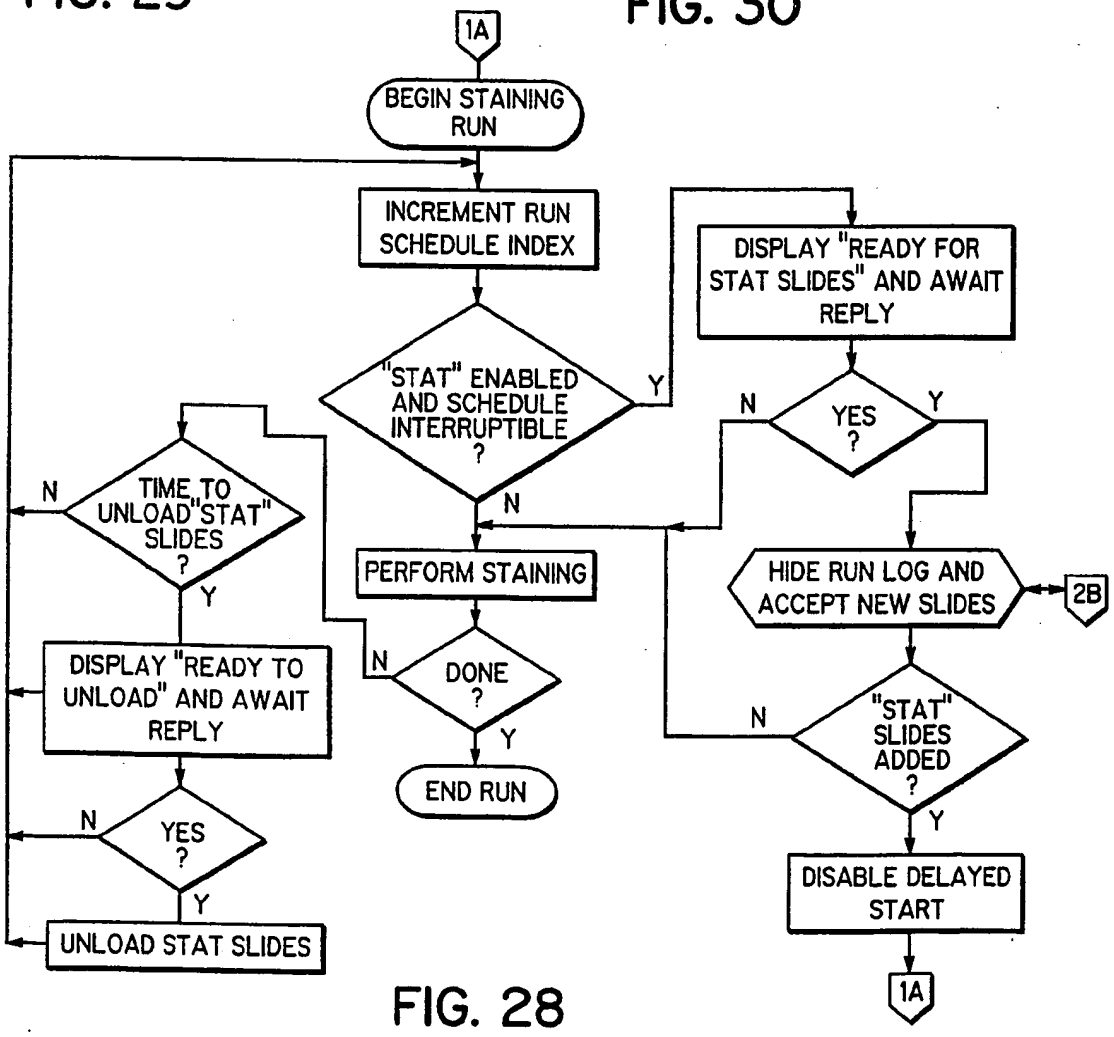

FIG. 28

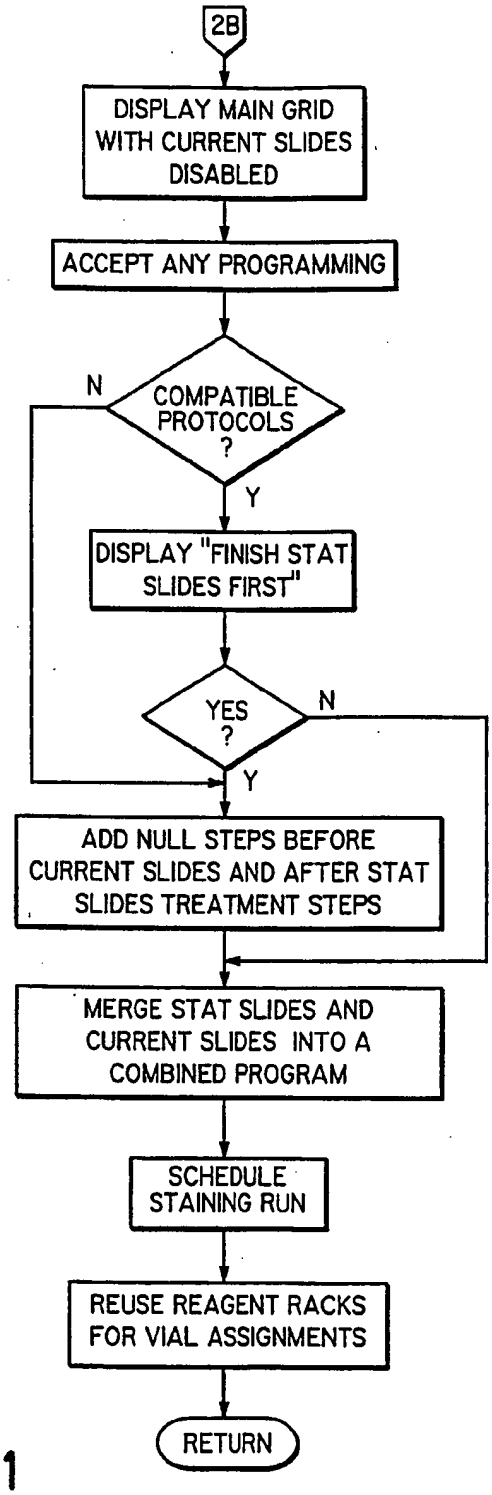
2B
DISPLAY MAIN GRID WITH CURRENT SLIDES DISABLED
ACCEPT ANY PROGRAMMING
COMPATIBLE PROTOCOLS ?
N
Y
DISPLAY "FINISH STAT SLIDES FIRST"
YES ?
N
Y
ADD NULL STEPS BEFORE CURRENT SLIDES AND AFTER STAT SLIDES TREATMENT STEPS
MERGE STAT SLIDES AND CURRENT SLIDES INTO A COMBINED PROGRAM
SCHEDULE STAINING RUN
REUSE REAGENT RACKS FOR VIAL ASSIGNMENTS
RETURN

FIG. 31

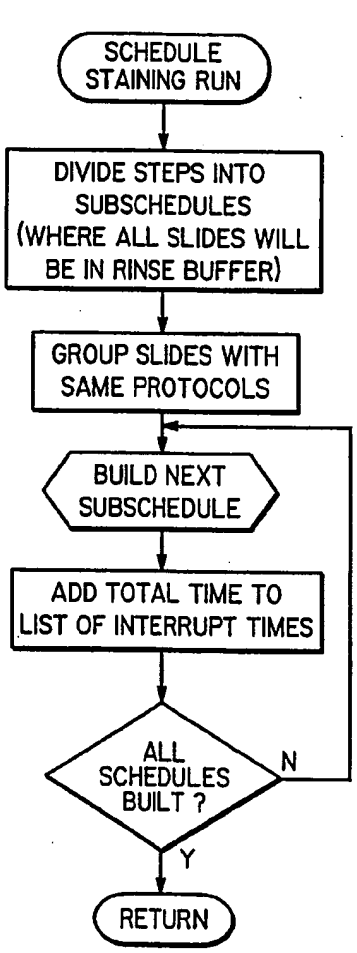

FIG. 32A

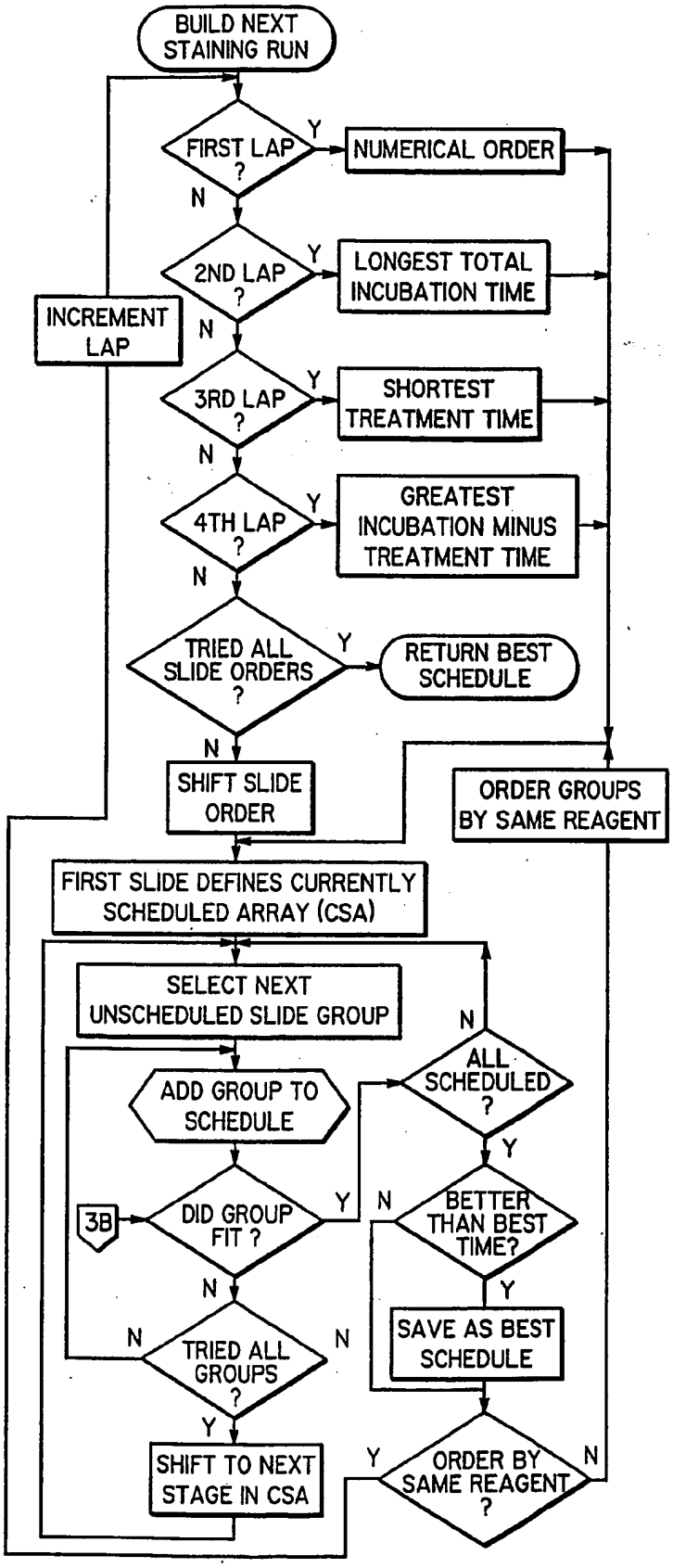

FIG. 32B

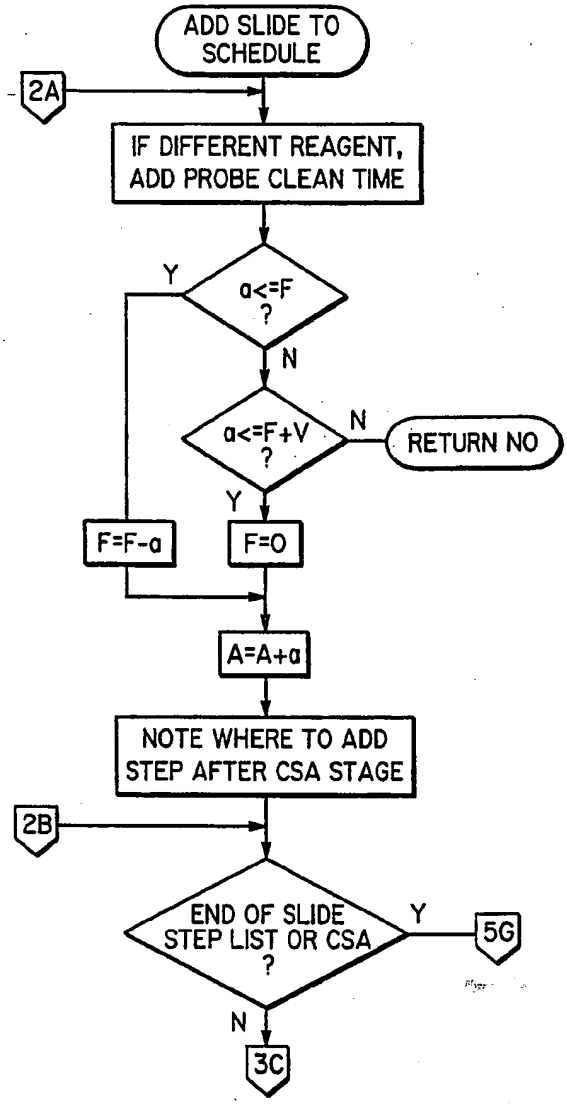
ADD SLIDE TO SCHEDULE
2A
IF DIFFERENT REAGENT, ADD PROBE CLEAN TIME
a<=F ?
Y
N
a<=F+V ?
N
RETURN NO
Y
F=F-a
F=0
A=A+a
NOTE WHERE TO ADD STEP AFTER CSA STAGE
2B
END OF SLIDE STEP LIST OR CSA ?
Y
5G
N
3C

FIG. 32C

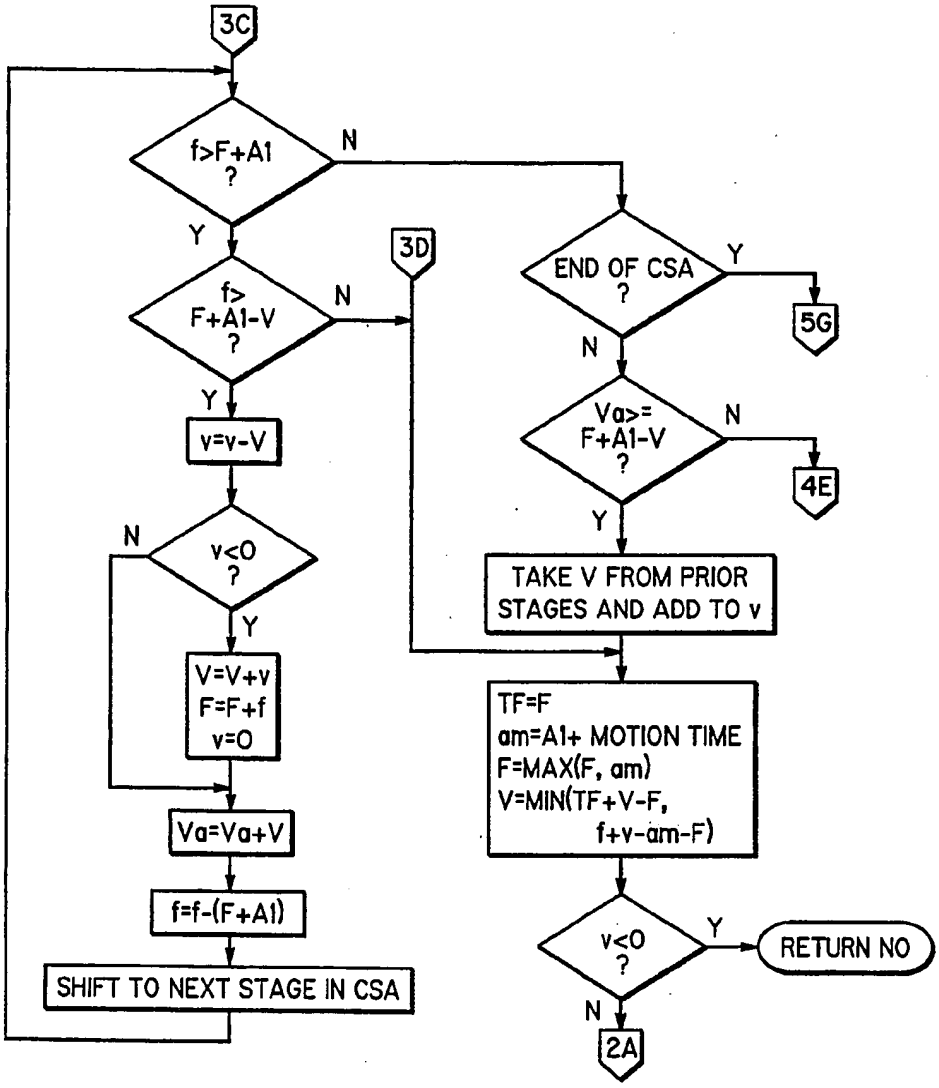
3C
f>F+A1 ?
N
Y
f> F+A1-V ?
N
3D
Y
v=v-V
N
v<0 ?
Y
V=V+v
F=F+f
v=0
Va=Va+V
f=f-(F+A1)
SHIFT TO NEXT STAGE IN CSA
END OF CSA ?
Y
5G
N
Va>= F+A1-V ?
N
4E
Y
TAKE V FROM PRIOR STAGES AND ADD TO v
TF=F
am=A1+ MOTION TIME
F=MAX(F, am)
V=MIN(TF+V-F, f+v-am-F)
v<0 ?
Y
RETURN NO
N
2A

FIG. 32D

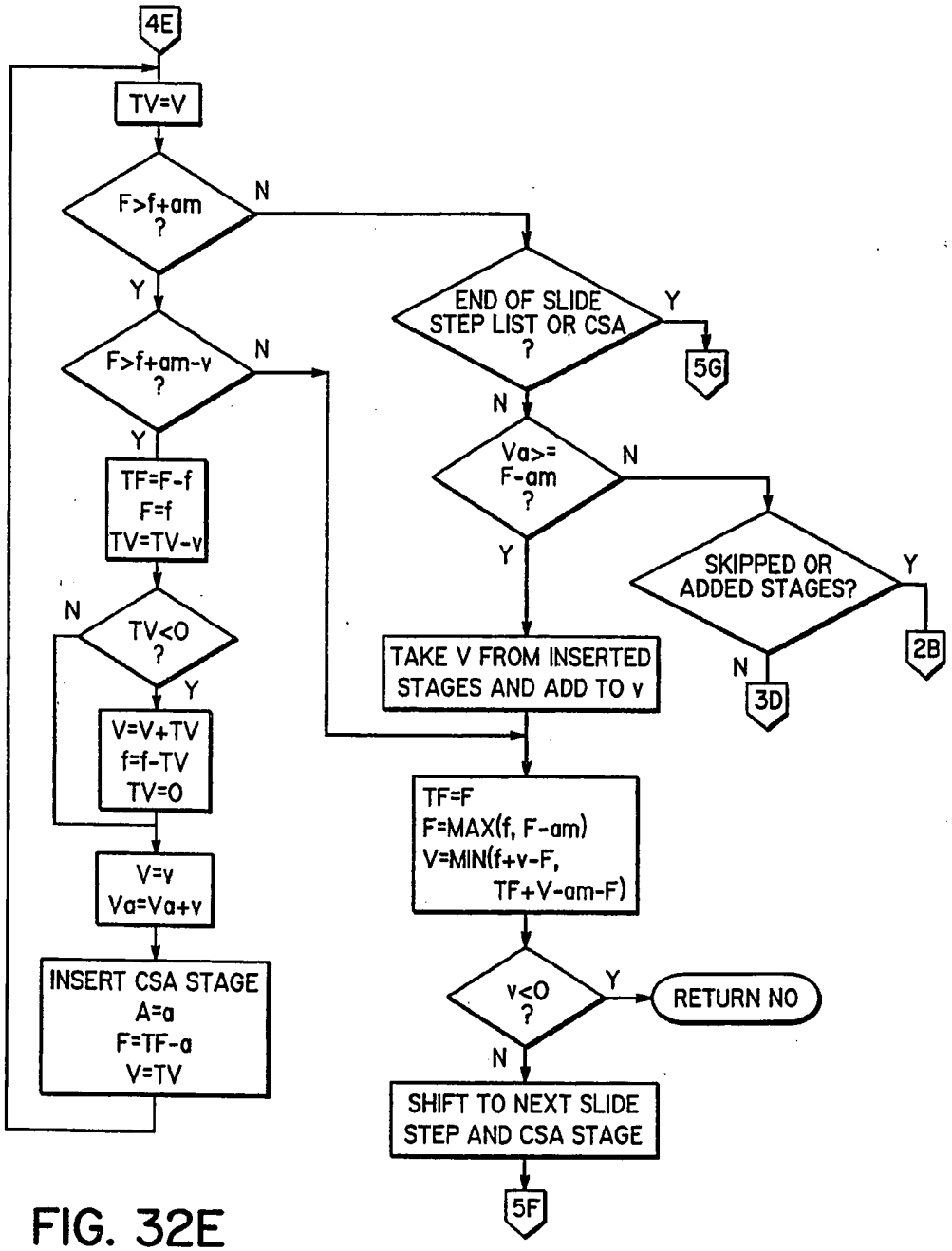
4E
TV=V
F>f+am ?
N
Y
F>f+am-v ?
N
Y
TF=F-f
F=f
TV=TV-v
N
TV<0 ?
Y
V=V+TV
f=f-TV
TV=0
V=v
Va=Va+v
INSERT CSA STAGE
A=a
F=TF-a
V=TV
END OF SLIDE STEP LIST OR CSA ?
Y
5G
N
Va>= F-am ?
N
Y
SKIPPED OR ADDED STAGES?
Y
2B
N
3D
TAKE V FROM INSERTED STAGES AND ADD TO v
TF=F
F=MAX(f, F-am)
V=MIN(f+v-F, TF+V-am-F)
v<0 ?
Y
RETURN NO
N
SHIFT TO NEXT SLIDE STEP AND CSA STAGE
5F

FIG. 32E

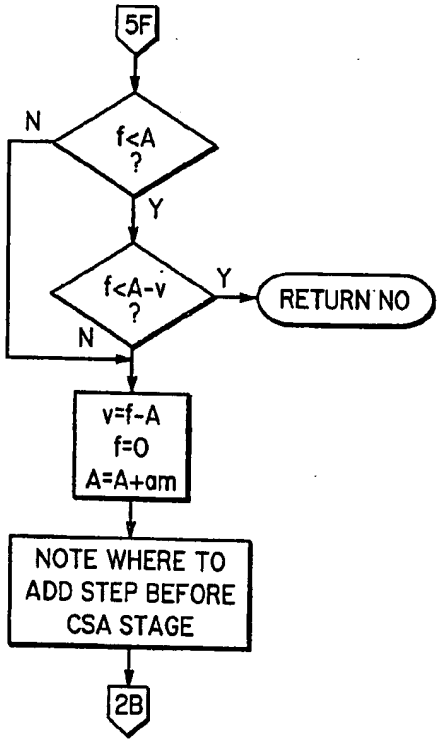

FIG. 32F

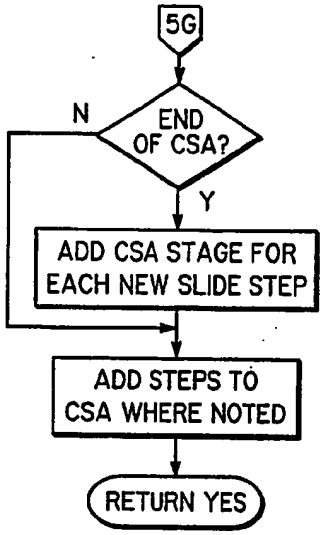

FIG. 32G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/36247

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N1/31

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 839 091 A (CORL MARK V ET AL) 17 November 1998 (1998-11-17) column 3-7 claims 1-23	9-28
Y	WO 01 51909 A (LAB VISION CORP) 19 July 2001 (2001-07-19) page 10, line 21 -page 16, line 22	9-28
A	WO 01 68259 A (BAHL SUNEET ;ZHANG JASON (US); BIOGENEX LAB (US); KALRA KRISHAN L) 20 September 2001 (2001-09-20) page 3, line 1-25 page 6, line 1 -page 7, line 5 page 14, line 14 -page 15, line 6	9-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2003	27/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Michalitsch, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/36247

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 559 032 A (POMEROY PATRICK C ET AL) 24 September 1996 (1996-09-24) column 4, line 24-67 figures 1-6,8,9	9-28
A	US 5 948 359 A (ZHANG JASON Z ET AL) 7 September 1999 (1999-09-07) column 4, line 37 -column 5, line 6 column 7, line 54 -column 8, line 46 column 16, line 46 -column 17, line 25 figure 17	9-28

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/36247

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-8
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-8

Claims searched in part: 15-25

I.)
Due to the only partially overlapping subject matter of the multiple independent claims and the concurrent lack of conciseness of the claim set as a whole, the subject matter for which protection is sought is not clearly defined. The multiple definitions in the independent claims place an undue burden on others seeking to establish the scope of the invention and the extend of protection. Therefore the application does not fulfill the requirements of Art. 6 PCT.

II.) The lack of clarity is compounded by unclear and contradictory definitions of the subject matter in the individual independent claims.

a)
Claim 1 relates to a computer program product comprising a computer usable medium (e.g. a CD etc.)
The features of claim 1, however, appear to relate to an apparatus (such as "means for providing a buffer, a reagent...). It is therefore unclear if the characterizing features of the claim relate to a computer usable medium or to a staining apparatus (or to a staining method).
Furthermore, in view of the description, claim 1 appears to lack an inventive feature that links the claim to the other independent claims, in breach of rule 13 PCT.

b)
Claim 28 refers to an apparatus for processing slides and appears to be the broadest apparatus claim. Claim 26, on the other hand, refers to an autostainer. Staining, however, is only one step in the (histochemical) preparation process. Therefore claim 26 appears to aim at a more restricted subject matter than claim 28, it should therefore depend thereon.
Furthermore, claim 28 relates to a robotic motion control system for controlling a "processing schedule", while claim 26 relates to a control program for executing protocol steps. The application therefore also risks to lack unity, in breach of rule 13 PCT.

In conclusion, the claimset as whole and the independent claims, in particular, are so unclear and so inconcise that a meaningful search of the subject matter across the whole range is impossible.
Thus, the application was searched insofar as the subject matter relates to:

- a method as claimed in claims 9 - 14,
- an apparatus as in claims 26-29, wherein both, the "processing schedule" of claim 28 and the "processing protocol" of claim 26 are considered to be part of a common program and hence

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

inseperable,
- and, a computer program product as claimed in claims 15 and 21 and the claims dependent thereon.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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